Calculations: Calculations were performed using Excel Version 8.0e. Some reported values may differ in the last reported digit from values calculated directly from the report tables due to the rounding that has been applied.

Pharmacokinetic Analysis: The maximum concentration (C_{max}) in rat plasma and the time to reach maximum concentration (T_{max}) were obtained by visual inspection of the raw data. Pharmacokinetic parameters calculated included half-life ($t_{1/2}$), time to maximum plasma concentration (T_{max}), area under the concentration-time curve from time 0 to the last time point (AUC_{0-t}), area under the concentration-time curve from 0 to infinity ($AUC_{0-\infty}$), volume of distribution (V_z), and clearance (CL). Pharmacokinetic parameters were calculated by using WinNonlin Professional Edition (Pharsight Corporation, Version 3.3).

Results and Conclusions

For gabapentin (Table 2), the elimination phase of the concentration vs. time profiles was not well defined. Based on the comparison of C_{max} and AUC_{0-t} data, there appeared to be no appreciable difference between the oxybutynin (Oxy) group and the combination (Com) group. No evidence of drug-drug interaction between oxybutynin and gabapentin was found with the current study design.

For oxybutynin (Table 3), the pharmacokinetic parameters (C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, $t_{1/2}$, V_z and CL) obtained from the combination (Com) group did not appear to be appreciably different than those from the oxybutynin (Oxy) group. No evidence of drug-drug interaction between oxybutynin and gabapentin was found with the current study design.

For desethyl oxybutynin (Table 4), the elimination phase of the concentration vs. time profile was not well defined. However, based on the comparison of C_{max} and AUC_{0-t} data, there again appeared to be no appreciable difference between the oxybutynin (Oxy) group and the combination (Com) group.

The results of the pharmacokinetic study indicate that pharmacokinetic influences of one drug on the other do not account for the synergistic nature of the oxybutynin-gabapentin combination as seen in Example 1. That is to say that the synergistic nature of the positive effect of the combination on lower urinary tract function is not due to some pharmacokinetic interaction.

Table 2
Pharmacokinetic parameters for gabapentin in rat plasma

Treatment	Animal	Dose Level (mg/kg)	C_{max} (ng/mL)	T_{max} (minutes)	AUC_{0-t} (min*ng/mL)	$AUC_{0-\infty}$ (min*ng/mL)	$t_{1/2}$ (minutes)	V_z (mL/kg)	CL (mL/min/kg)
Com	7	100	1.13E+05	60	1.26E+07	NC	NC	NC	NC
Com	8	100	1.01E+05	30	1.08E+07	4.59E+07	303	951	2.18
Com	9	100	9.33E+04	15	1.05E+07	7.06E+07	519	1060	1.42
Com	10	100	1.03E+05	15	8.76E+06	1.51E+07	97.3	928	6.61
Com	11	100	1.56E+05	60	1.40E+07	NC	NC	NC	NC
Com	20	100	1.00E+05	15	1.07E+07	NC	NC	NC	NC
Com	23	100	1.12E+05	15	1.10E+07	4.39E+07	296	975	2.28
Com	24	100	1.03E+05	30	1.16E+07	NC	NC	NC	NC
Mean			1.10E+05		1.13E+07	4.39E+07	304	978	3.12
SD			1.96E+04		1.56E+06	2.27E+07	172	57.4	2.36
Gab	4	100	1.07E+05	15	1.25E+07	NC	NC	NC	NC
Gab	5	100	1.12E+05	15	1.02E+07	1.95E+07	116	857	5.12
Gab	6	100	1.07E+05	15	8.56E+06	1.37E+07	86.2	910	7.32
Gab	12	100	1.10E+05	15	1.01E+07	2.19E+07	135	890	4.57
Gab	13	100	9.52E+04	15	8.19E+06	1.44E+07	99.4	996	6.95
Gab	14	100	1.23E+05	120	1.28E+07	NC	NC	NC	NC
Gab	17	100	*3.45E+01	120	*2.12E+03	NC	NC	NC	NC
Gab	21	100	3.59E+04	30	3.80E+06	1.16E+07	205	2555	8.63
Mean			9.86E+04		9.45E+06	1.62E+07	128	1242	6.52
SD			2.88E+04		3.05E+06	4.32E+06	46.7	736	1.66

$AUC_{0-\infty}$ Area under the plasma concentration-time curve up to infinity.
AUC_{0-t} Area under the plasma concentration-time curve up to the last sampling time with measurable concentrations.
CL Clearance.
C_{max} Maximum plasma concentration.
NA Not applicable.
NC Not calculated due to insufficient elimination phase data.
SD Standard deviation.
$t_{1/2}$ Observed elimination half-life.
T_{max} Time to maximum concentration.
V_z Volume of distribution.
* Outliers. Excluded from mean and SD calculations.

Table 3
Pharmacokinetic parameters for oxybutynin in rat plasma

Treatment	Animal	Dose Level (mg/kg)	C_{max} (ng/mL)	T_{max} (minutes)	AUC_{0-t} (min*ng/mL)	$AUC_{0-\infty}$ (min*ng/mL)	$t_{1/2}$ (minutes)	V_z (mL/kg)	CL (mL/min/kg)
Com	7	3	320	15	22152	28177	24.6	3774	106
Com	8	3	360	15	20737	23114	39.3	7363	130
Com	9	3	248	15	16201	19116	45.5	10301	157
Com	10	3	316	15	18387	20541	39.9	8411	146
Com	11	3	282	15	16057	18295	43.3	10252	164
Com	20	3	367	15	21889	26725	53.0	8590	112
Com	23	3	342	15	19405	21702	41.5	8270	138
Com	24	3	295	15	17222	19529	41.2	9136	154
Mean			316		19006	22150	41.0	8262	138
SD			40.4		2435	3624	7.97	2069	20.9
Oxy	1	3	228	15	15566	21438	72.8	14701	140
Oxy	2	3	448	15	24555	28547	55.6	8425	105
Oxy	3	3	238	15	12865	14181	39.8	12158	212
Oxy	15	3	217	15	15880	20477	56.8	12004	147
Oxy	16	3	419	15	23333	24944	32.5	5632	120
Oxy	18	3	426	15	28295	38044	66.9	7612	78.9
Mean			329		20082	24605	54	10089	134
SD			112		6135	8149	15.5	3405	45.3

$AUC_{0-\infty}$ Area under the plasma concentration-time curve up to infinity.
AUC_{0-t} Area under the plasma concentration-time curve up to the last sampling time with measurable concentrations.
CL Clearance.
C_{max} Maximum plasma concentration.
NA Not applicable.
NC Not calculated due to insufficient elimination phase data.
SD Standard deviation.
$t_{1/2}$ Observed elimination half-life.
T_{max} Time to maximum concentration.
V_z Volume of distribution.

Table 4
Pharmacokinetic parameters for desethyl oxybutynin in rat plasma

Treatment	Animal	Dose Level (mg/kg)	C_{max} (ng/mL)	T_{max} (minutes)	AUC_{0-t} (min*ng/mL)	$AUC_{0-\infty}$ (min*ng/mL)	$t_{1/2}$ (minutes)	V_z (mL/kg)	CL (mL/min/kg)
Com	7	3	1.19	15	68.0	471	266	2444603	6370
Com	8	3	1.15	15	65.5	495	292	2551693	6066
Com	9	3	1.57	30	176	877	365	1801875	3420
Com	10	3	1.71	15	163	404	167	1788610	7426
Com	11	3	1.47	15	80.9	301	133	1907790	9965
Com	20	3	3.84	15	345	880	158	776714	3408
Com	23	3	3.23	15	264	493	113	992758	6088
Com	24	3	1.80	15	177	442	160	1563846	6788
Mean			2.00		168	545	207	1728486	6191
SD			0.99		99.1	215	89.7	621739	2125
Oxy	1	3	3.6	15	306	716	158	954133	4191
Oxy	2	3	1.55	15	47.7	99	32.0	1392698	30168
Oxy	3	3	1.7	15	53.4	92	24.4	1142356	32463
Oxy	15	3	1.18	60	69.7	NC	NC	NC	NC
Oxy	16	3	1.59	15	83.9	247	100	1754810	12124
Oxy	18	3	2.81	120	306	NC	NC	NC	NC
Mean			2.07		144	289	78.6	1310999	19737
SD			0.93		126	293	62.9	346139	13789

$AUC_{0-\infty}$ Area under the plasma concentration-time curve up to infinity.
AUC_{0-t} Area under the plasma concentration-time curve up to the last sampling time with measurable concentrations.
CL Clearance.
C_{max} Maximum plasma concentration.
NA Not applicable.
NC Not calculated due to insufficient elimination phase data.
SD Standard deviation.
$t_{1/2}$ Observed elimination half-life.
T_{max} Time to maximum concentration.
V_z Volume of distribution.

Example 3 – Dilute Acetic Acid Model: Pregabalin and Oxybutynin

Objective and Rationale

The objective of this study was to determine the ability of an $\alpha_2\delta$ subunit calcium channel modulator in combination with a smooth muscle modulator to reverse the reduction in bladder capacity seen following continuous infusion of dilute acetic acid, a commonly used model of overactive bladder. In particular, the current study utilized pregabalin as an exemplary $\alpha_2\delta$ subunit calcium channel modulator, and oxybutynin as an exemplary a smooth muscle modulator.

Materials and Methods

Urethane anesthetized (1.2 g/kg) normal female rats were utilized in this study. Groups of rats were treated with oxybutynin alone, pregabalin alone, and respective dose–matched combinations of oxybutynin and pregabalin.

Drugs and Preparation

In one series of studies, drugs were dissolved in normal saline at 1, 3 and 10 mg/ml for oxybutynin and 10, 30 and 100 mg/ml for pregabalin. In these studies, individual doses and combinations may be subsequently referred to as Low, Mid and High. Animals were dosed by volume of injection = body weight in kg.

In another series of studies, drugs were dissolved in normal saline at 0.625, 1.25, 2.5, 5.0 and 10 mg/ml for oxybutynin and 3.75, 7.5, 15, 30 and 60 mg/ml for pregabalin. In these studies, individual doses and combinations may be subsequently referred to as Low, Mid Low, Mid, Mid High and High. Animals were dosed by volume of injection = body weight in kg.

Acute Anesthetized In Vivo Model

Animal Preparation: Female rats (250-300 g body weight) were anesthetized with urethane (1.2 g/kg) and a saline-filled catheter (PE-50) was inserted into the jugular vein for intravenous drug administration. Via a midline lower abdominal incision, a flared-tipped PE 50 catheter was inserted into the bladder dome for bladder filling and pressure recording. The abdominal cavity was moistened with saline and closed by covering with a thin plastic sheet in order to maintain access to the bladder for emptying purposes. Fine silver or stainless steel wire electrodes were inserted into the external urethral sphincter (EUS) percutaneously for electromyography (EMG).

Experimental Design: Saline was continuously infused at a rate of 0.055 ml/min via the bladder-filling catheter for 60 minutes to obtain a baseline of lower urinary tract activity (continuous cystometry; CMG). Following the control period, a 0.25% acetic acid solution in saline was infused into the bladder at the same flow rate to induce bladder irritation. Following 30 minutes of AA infusion, 3 vehicle injections were made at 20 minute intervals to determine vehicle effects, if any.

Subsequently, increasing doses of a selected active agent, or combination of agents, at half log increments were administered intravenously at 30 minute intervals in order to construct a cumulative dose-response relationship. At the end of the control saline cystometry period, the third vehicle, and 20 minutes following each subsequent treatment, the infusion pump was stopped, the bladder was emptied by fluid withdrawal via the infusion catheter and a single filling cystometrogram was performed at the same flow rate in order to determine changes in bladder capacity caused by the irritation protocol and subsequent intravenous drug administration.

Data Analysis

Bladder capacity data for each animal were normalized to "% Recovery from Irritation," and this index was used as the measure of efficacy. Data from experiments in which each of the drugs were administered alone were utilized to create theoretical populations of additive effects for each dose (low, mid and high), and these were compared by one-tailed t-test (individual dose comparisons) and by 2-Way ANOVA (across doses) to the actual combination drug data. The means and standard deviations of each individual treatment's "dose-matched" (low, middle, and high) responses were added together to estimate the mean and standard deviation of the theoretical additive populations for which to compare to the actual data obtained from the combination experiments. The theoretical additive effect population $N = (N_{antimuscarinic} + N_{\alpha2\delta\ subunit\ modulator}) - 1$. $P<0.050$ was considered significant. Only rats that showed between a 50-90% reduction in bladder capacity at the third vehicle measurement when compared to pre-irritation saline control values were utilized for numerical analyses.

Results and Conclusions

The effect of cumulative increasing doses of oxybutynin (n=13), pregabalin (n=7) and matched combinations (e.g. Dose 1 for the combination was 10 mg/kg pregabalin and 1 mg/kg oxybutynin; n=9) on bladder capacity is depicted in Figure 5. Data are normalized to saline controls and are presented as Mean ± SEM.

The effect of cumulative increasing doses of oxybutynin (n=13), pregabalin (n=7) and matched combinations (e.g. Dose 1 for the combination was 10 mg/kg pregabalin and 1 mg/kg oxybutynin; n=9) on bladder capacity (normalized to %

Recovery from Irritation) is depicted in Figure 6. Data are presented as Mean ± SEM. Note that the combination of drugs produced a greater than additive effect at the Low (P=0.0386), Mid (P=0.0166) and High doses (P=0.0098), on reduction in bladder capacity caused by continuous intravesical exposure to dilute acetic acid Synergy is also suggested by significant differences between Additive and Combination effects by 2-Way ANOVA (P<0.0004).

The effect of cumulative increasing doses of oxybutynin (n=4), pregabalin (n=7) and matched combinations (e.g. Dose 1 for the combination was 3.75 mg/kg pregabalin and 0.625 mg/kg oxybutynin; n=4) on bladder capacity is depicted in Figure 7. Data are normalized to saline controls and are presented as Mean ± SEM.

The effect of cumulative increasing doses of oxybutynin (n=4), pregabalin (n=7) and their matched combinations (e.g. Dose 1 for the combination was 3.75 mg/kg pregabalin and 0.625 mg/kg oxybutynin; n=4) on bladder capacity (normalized to % Recovery from Irritation) is depicted in Figure 8. Data are presented as Mean ± SEM. Note also that the combination of drugs produced a greater than additive effect at the Mid High (P=0.04) and High doses (P=0.004) on reduction in bladder capacity caused by continuous intravesical exposure to dilute acetic acid. Synergy is also suggested by significant differences between Additive and Combination effects by 2-Way ANOVA (P=0.0037).

The ability of an $\alpha_2\delta$ subunit calcium channel modulator in combination with a smooth muscle modulator to produce a dramatic reversal in acetic acid irritation-induced reduction in bladder capacity strongly indicates efficacy in mammalian forms of painful and non-painful and associated irritative symptoms lower urinary tract disorders in normal and spinal cord injured patients. Furthermore, the combination of an $\alpha_2\delta$ subunit calcium channel modulator and a smooth muscle modulator produced a synergistic effect that was greater than what would be expected if the effects were simply additive.

Example 4 – Dilute Acetic Acid Model: Gabapentin and Tolterodine

Objective and Rationale

The objective of this study was to determine the ability of an $\alpha_2\delta$ subunit calcium channel modulator in combination with a smooth muscle modulator to

reverse the reduction in bladder capacity seen following continuous infusion of dilute acetic acid, a commonly used model of overactive bladder. In particular, the current study utilized gabapentin as an exemplary $\alpha_2\delta$ subunit calcium channel modulator, and tolterodine as an exemplary a smooth muscle modulator.

Materials and Methods

Urethane anesthetized (1.2 g/kg) normal female rats were utilized in this study. Groups of rats were treated with tolterodine alone (n=9), gabapentin alone (n=11), and 2 combination studies characterized by single initial dose combinations of tolterodine (Mid and High) together with the Low dose of gabapentin, followed in turn by the Mid and High doses of gabapentin alone (n=4 and n=3, respectively).

Drugs and Preparation

Drugs were dissolved in normal saline at 1, 3 and 10 mg/ml for tolterodine and 10, 30 and 100 mg/ml for gabapentin. In these studies, individual doses may be subsequently referred to as Low, Mid and High. Combinations are referred to as 3 mg/kg Tolt. Combination and 10 mg/kg Tolt. Combination. Animals were dosed by volume of injection = body weight in kg.

Acute Anesthetized In Vivo Model

Animal Preparation: Female rats (250-300 g body weight) were anesthetized with urethane (1.2 g/kg) and a saline-filled catheter (PE-50) was inserted into the jugular vein for intravenous drug administration. Via a midline lower abdominal incision, a flared-tipped PE 50 catheter was inserted into the bladder dome for bladder filling and pressure recording. The abdominal cavity was moistened with saline and closed by covering with a thin plastic sheet in order to maintain access to the bladder for emptying purposes. Fine silver or stainless steel wire electrodes were inserted into the external urethral sphincter (EUS) percutaneously for electromyography (EMG).

Experimental Design: Saline was continuously infused at a rate of 0.055 ml/min via the bladder-filling catheter for 60 minutes to obtain a baseline of lower urinary tract activity (continuous cystometry; CMG). Following the control period, a

0.25% acetic acid solution in saline was infused into the bladder at the same flow rate to induce bladder irritation. Following 30 minutes of AA infusion, 3 vehicle injections were made at 20 minute intervals to determine vehicle effects, if any. Subsequently, increasing doses of a selected active agent, or combination of agents, at half log increments were administered intravenously at 30 minute intervals in order to construct a cumulative dose-response relationship. At the end of the control saline cystometry period, the third vehicle, and 20 minutes following each subsequent treatment, the infusion pump was stopped, the bladder was emptied by fluid withdrawal via the infusion catheter and a single filling cystometrogram was performed at the same flow rate in order to determine changes in bladder capacity caused by the irritation protocol and subsequent intravenous drug administration.

Data Analysis

Bladder capacity data for each animal were normalized to "% Recovery from Irritation," and this index was used as the measure of efficacy. Data from experiments in which each of the drugs were administered alone were utilized to create theoretical populations of additive effects for each dose (low, mid and high), and these were compared by one-tailed t-test (individual dose comparisons) and by 2-Way ANOVA (across doses) to the actual combination drug data. The means and standard deviations of each individual treatment's "dose-matched" (low, middle, and high) responses were added together to estimate the mean and standard deviation of the theoretical additive populations for which to compare to the actual data obtained from the combination experiments. The theoretical additive effect population $N = (N_{antimuscarinic} + N_{\alpha 2\delta\ subunit\ modulator}) - 1$. $P<0.050$ was considered significant. Only rats that showed between a 50-90% reduction in bladder capacity at the third vehicle measurement when compared to pre-irritation saline control values were utilized for numerical analyses.

Results and Conclusions

The effect of cumulative increasing doses of tolterodine (n=9), gabapentin (n=11) and the 2 combinations tested (e.g. Dose 1 for the combination 1 was 30 mg/kg gabapentin and 3 mg/kg tolterodine; n=4 and 3 for 3 and 10 mg/kg tolterodine,

respectively) on bladder capacity is depicted in Figure 9. Data are normalized to saline controls and are presented as Mean ± SEM.

The effect of cumulative increasing doses of tolterodine (n=9), gabapentin (n=11) and the 2 combinations (e.g. Dose 1 for the combination was 30 mg/kg gabapentin and 3 mg/kg tolterodine; n=4 and 3, for 3 mg/kg and 10 mg/kg tolterodine, respectively) on bladder capacity (normalized to % Recovery from Irritation) is depicted in Figure 10. Data are presented as Mean ± SEM. Note that the combination of drugs produced a greater than additive effect for the 3 mg/kg Tolt. Combination (P=0.0099) and the 10 mg/kg Tolt. Combination (P=0.0104).

The ability of an $\alpha_2\delta$ subunit calcium channel modulator in combination with a smooth muscle modulator to produce a dramatic reversal in acetic acid irritation-induced reduction in bladder capacity strongly indicates efficacy in mammalian forms of painful and non-painful lower urinary tract disorders and associated irritative symptoms in normal and spinal cord injured patients. Furthermore, the combination of an $\alpha_2\delta$ subunit calcium channel modulator and a smooth muscle modulator produced a synergistic effect that was greater than what would be expected if the effects were simply additive.

Example 5 – Dilute Acetic Acid Model: Pregabalin and Tolterodine

Objective and Rationale

The objective of this study was to determine the ability of an $\alpha_2\delta$ subunit calcium channel modulator in combination with a smooth muscle modulator to reverse the reduction in bladder capacity seen following continuous infusion of dilute acetic acid, a commonly used model of overactive bladder. In particular, the current study utilized pregabalin as an exemplary $\alpha_2\delta$ subunit calcium channel modulator, and tolterodine as an exemplary a smooth muscle modulator.

Materials and Methods

Urethane anesthetized (1.2 g/kg) normal female rats were utilized in this study. Groups of rats were treated with tolterodine alone (n=9), pregabalin alone

(n=7), and respective dose--matched combinations of tolterodine and pregabalin (n=9).

Drugs and Preparation

Drugs were dissolved in normal saline at 1, 3 and 10 mg/ml for tolterodine and 10, 30 and 100 mg/ml for pregabalin. In these studies, individual doses and combinations may be subsequently referred to as Low, Mid and High. Animals were dosed by volume of injection = body weight in kg.

Acute Anesthetized In Vivo Model

Animal Preparation: Female rats (250-300 g body weight) were anesthetized with urethane (1.2 g/kg) and a saline-filled catheter (PE-50) was inserted into the jugular vein for intravenous drug administration. Via a midline lower abdominal incision, a flared-tipped PE 50 catheter was inserted into the bladder dome for bladder filling and pressure recording. The abdominal cavity was moistened with saline and closed by covering with a thin plastic sheet in order to maintain access to the bladder for emptying purposes. Fine silver or stainless steel wire electrodes were inserted into the external urethral sphincter (EUS) percutaneously for electromyography (EMG).

Experimental Design: Saline was continuously infused at a rate of 0.055 ml/min via the bladder-filling catheter for 60 minutes to obtain a baseline of lower urinary tract activity (continuous cystometry; CMG). Following the control period, a 0.25% acetic acid solution in saline was infused into the bladder at the same flow rate to induce bladder irritation. Following 30 minutes of AA infusion, 3 vehicle injections were made at 20 minute intervals to determine vehicle effects, if any. Subsequently, increasing doses of a selected active agent, or combination of agents, at half log increments were administered intravenously at 30 minute intervals in order to construct a cumulative dose-response relationship. At the end of the control saline cystometry period, the third vehicle, and 20 minutes following each subsequent treatment, the infusion pump was stopped, the bladder was emptied by fluid withdrawal via the infusion catheter and a single filling cystometrogram was

performed at the same flow rate in order to determine changes in bladder capacity caused by the irritation protocol and subsequent intravenous drug administration.

Data Analysis

Bladder capacity data for each animal were normalized to "% Recovery from Irritation," and this index was used as the measure of efficacy. Data from experiments in which each of the drugs were administered alone were utilized to create theoretical populations of additive effects for each dose (low, mid and high), and these were compared by one-tailed t-test (individual dose comparisons) and by 2-Way ANOVA (across doses) to the actual combination drug data. The means and standard deviations of each individual treatment's "dose-matched" (low, middle, and high) responses were added together to estimate the mean and standard deviation of the theoretical additive populations for which to compare to the actual data obtained from the combination experiments. The theoretical additive effect population $N = (N_{antimuscarinic} + N_{\alpha2\delta\ subunit\ modulator}) - 1$. $P<0.050$ was considered significant. Only rats that showed between a 50-90% reduction in bladder capacity at the third vehicle measurement when compared to pre-irritation saline control values were utilized for numerical analyses.

Results and Conclusions

The effect of cumulative increasing doses of tolterodine (n=9), pregabalin (n=7) and their matched combinations (e.g. Dose 1 for the combination was 10 mg/kg pregabalin and 1 mg/kg tolterodine; n=9) on bladder capacity is depicted in Ficure 11. Data are normalized to saline controls and are presented as Mean ± SEM.

The effect of cumulative increasing doses of tolterodine (n=9), pregabalin (n=7) and matched combinations (e.g. Dose 1 for the combination was 10 mg/kg pregabalin and 1 mg/kg tolterodine; n=9) on bladder capacity (normalized to % Recovery from Irritation) is depicted in Figure 12. Data are presented as Mean ± SEM. Note also that the combination of drugs produced a greater than additive effect at the Mid doses (P=0.0353) on reduction in bladder capacity caused by continuous intravesical exposure to dilute acetic acid. Synergy is also suggested by significant differences between Additive and Combination effects by 2-Way ANOVA (P<0.0234).

The ability of an $\alpha_2\delta$ subunit calcium channel modulator in combination with a smooth muscle modulator to produce a dramatic reversal in acetic acid irritation-induced reduction in bladder capacity strongly indicates efficacy in mammalian forms of painful and non-painful lower urinary tract disorders and associated irritative symptoms in normal and spinal cord injured patients. Furthermore, the combination of an $\alpha_2\delta$ subunit calcium channel modulator and a smooth muscle modulator produced a synergistic effect that was greater than what would be expected if the effects were simply additive.

Example 6 – Dilute Acetic Acid Model: Gabapentin and Propiverine

Objective and Rationale

The objective of this study was to determine the ability of an $\alpha_2\delta$ subunit calcium channel modulator in combination with a smooth muscle modulator to reverse the reduction in bladder capacity seen following continuous infusion of dilute acetic acid, a commonly used model of overactive bladder. In particular, the current study utilized gabapentin as an exemplary $\alpha_2\delta$ subunit calcium channel modulator, and propiverine as an exemplary a smooth muscle modulator.

Materials and Methods

Urethane anesthetized (1.2 g/kg) normal female rats were utilized in this study. Groups of rats were treated with propiverine alone (n=7), gabapentin alone (n=11), and respective dose–matched combinations of propiverine and gabapentin (n=10).

Drugs and Preparation

Drugs were dissolved in normal saline at 3, 10 and 30 mg/ml for propiverine and 10, 30 and 100 mg/ml for gabapentin. In these studies, individual doses and combinations may be subsequently referred to as Low, Mid and High. Animals were dosed by volume of injection = body weight in kg.

Acute Anesthetized In Vivo Model

Animal Preparation: Female rats (250-300 g body weight) were anesthetized with urethane (1.2 g/kg) and a saline-filled catheter (PE-50) was inserted into the jugular vein for intravenous drug administration. Via a midline lower abdominal incision, a flared-tipped PE 50 catheter was inserted into the bladder dome for bladder filling and pressure recording. The abdominal cavity was moistened with saline and closed by covering with a thin plastic sheet in order to maintain access to the bladder for emptying purposes. Fine silver or stainless steel wire electrodes were inserted into the external urethral sphincter (EUS) percutaneously for electromyography (EMG).

Experimental Design: Saline was continuously infused at a rate of 0.055 ml/min via the bladder-filling catheter for 60 minutes to obtain a baseline of lower urinary tract activity (continuous cystometry; CMG). Following the control period, a 0.25% acetic acid solution in saline was infused into the bladder at the same flow rate to induce bladder irritation. Following 30 minutes of AA infusion, 3 vehicle injections were made at 20 minute intervals to determine vehicle effects, if any. Subsequently, increasing doses of a selected active agent, or combination of agents, at half log increments were administered intravenously at 30 minute intervals in order to construct a cumulative dose-response relationship. At the end of the control saline cystometry period, the third vehicle, and 20 minutes following each subsequent treatment, the infusion pump was stopped, the bladder was emptied by fluid withdrawal via the infusion catheter and a single filling cystometrogram was performed at the same flow rate in order to determine changes in bladder capacity caused by the irritation protocol and subsequent intravenous drug administration.

Data Analysis

Bladder capacity data for each animal were normalized to "%Irritation Control," and this index was used as the measure of efficacy. Data from experiments in which each of the drugs were administered alone were utilized to create theoretical populations of additive effects for each dose (low, mid and high), and these were compared by one-tailed t-test (individual dose comparisons) and by 2-Way ANOVA (across doses) to the actual combination drug data. The means and standard

deviations of each individual treatment's "dose-matched" (low, middle, and high) responses were added together to estimate the mean and standard deviation of the theoretical additive populations for which to compare to the actual data obtained from the combination experiments. The theoretical additive effect population N = $(N_{antimuscarinic} + N_{\alpha 2\delta\ subunit\ modulator}) - 1$. $P<0.050$ was considered significant. Only rats that showed between a 50-90% reduction in bladder capacity at the third vehicle measurement when compared to pre-irritation saline control values were utilized for numerical analyses.

Results and Conclusions

The effect of cumulative increasing doses of propiverine (n=7), gabapentin (n=11) and their matched combinations (e.g. Dose 1 for the combination was 10 mg/kg gabapentin and 3 mg/kg propiverine; n=10) on bladder capacity is depicted in Figure 13. Data are normalized to saline controls and are presented as Mean ± SEM.

The effect of cumulative increasing doses of propiverine (n=7), gabapentin (n=11) and their matched combinations (e.g. Dose 1 for the combination was 10 mg/kg gabapentin and 3 mg/kg propiverine; n=10) on bladder capacity (normalized to % Recovery from Irritation) is depicted in Figure 14. Data are presented as Mean ± SEM. Note that the combination of drugs produced a greater than additive effect at the Low (P=0.0087) and Mid doses (P=0.0253) on reduction in bladder capacity caused by continuous intravesical exposure to dilute acetic acid. Synergy is also suggested by significant differences between Additive and Combination effects by 2-Way ANOVA ($P<0.0067$).

The ability of an $\alpha_2\delta$ subunit calcium channel modulator in combination with a smooth muscle modulator to produce a dramatic reversal in acetic acid irritation-induced reduction in bladder capacity strongly indicates efficacy in mammalian forms of painful and non-painful lower urinary tract disorders and associated irritative symptoms in normal and spinal cord injured patients. Furthermore, the combination of an $\alpha_2\delta$ subunit calcium channel modulator and a smooth muscle modulator produced a synergistic effect that was greater than what would be expected if the effects were simply additive.

Example 7 – Dilute Acetic Acid Model: Gabapentin and Solifenacin

Objective and Rationale

The objective of this study was to determine the ability of an $\alpha_2\delta$ subunit calcium channel modulator in combination with a smooth muscle modulator to reverse the reduction in bladder capacity seen following continuous infusion of dilute acetic acid, a commonly used model of overactive bladder. In particular, the current study utilized gabapentin as an exemplary $\alpha_2\delta$ subunit calcium channel modulator, and solifenacin as an exemplary a smooth muscle modulator.

Materials and Methods

Urethane anesthetized (1.2 g/kg) normal female rats were utilized in this study. Groups of rats were treated with solifenacin alone (n=7), gabapentin alone (n=11), and respective dose–matched combinations of solifenacin and gabapentin (n=10).

Drugs and Preparation

Drugs were dissolved in normal saline at 1, 3 and 10 mg/ml for solifenacin and 10, 30 and 100 mg/ml for gabapentin. In these studies, individual doses and combinations may be subsequently referred to as Low, Mid and High. Animals were dosed by volume of injection = (body weight in kg) * 1.5.

Acute Anesthetized In Vivo Model

Animal Preparation: Female rats (250-300 g body weight) were anesthetized with urethane (1.2 g/kg) and a saline-filled catheter (PE-50) was inserted into the jugular vein for intravenous drug administration. Via a midline lower abdominal incision, a flared-tipped PE 50 catheter was inserted into the bladder dome for bladder filling and pressure recording. The abdominal cavity was moistened with saline and closed by covering with a thin plastic sheet in order to maintain access to the bladder for emptying purposes. Fine silver or stainless steel wire electrodes were inserted into the external urethral sphincter (EUS) percutaneously for electromyography (EMG).

Experimental Design: Saline was continuously infused at a rate of 0.055 ml/min via the bladder-filling catheter for 60 minutes to obtain a baseline of lower urinary tract activity (continuous cystometry; CMG). Following the control period, a 0.25% acetic acid solution in saline was infused into the bladder at the same flow rate to induce bladder irritation. Following 30 minutes of AA infusion, 3 vehicle injections were made at 20 minute intervals to determine vehicle effects, if any. Subsequently, increasing doses of a selected active agent, or combination of agents, at half log increments were administered intravenously at 30 minute intervals in order to construct a cumulative dose-response relationship. At the end of the control saline cystometry period, the third vehicle, and 20 minutes following each subsequent treatment, the infusion pump was stopped, the bladder was emptied by fluid withdrawal via the infusion catheter and a single filling cystometrogram was performed at the same flow rate in order to determine changes in bladder capacity caused by the irritation protocol and subsequent intravenous drug administration.

Data Analysis

Bladder capacity data for each animal were normalized to "% Recovery from Irritation," and this index was used as the measure of efficacy. Data from experiments in which each of the drugs were administered alone were utilized to create theoretical populations of additive effects for each dose (low, mid and high), and these were compared by one-tailed t-test (individual dose comparisons) and by 2-Way ANOVA (across doses) to the actual combination drug data. The means and standard deviations of each individual treatment's "dose-matched" (low, middle, and high) responses were added together to estimate the mean and standard deviation of the theoretical additive populations for which to compare to the actual data obtained from the combination experiments. The theoretical additive effect population $N = (N_{antimuscarinic} + N_{\alpha2\delta\ subunit\ modulator}) - 1$. $P<0.050$ was considered significant. Only rats that showed between a 50-90% reduction in bladder capacity at the third vehicle measurement when compared to pre-irritation saline control values were utilized for numerical analyses.

Results and Conclusions

The effect of cumulative increasing doses of solifenacin (n=4), gabapentin (n=11) and their matched combinations (e.g. Dose 1 for the combination was 10

mg/kg gabapentin and 3 mg/kg solifenacin; n=12) on bladder capacity is depicted in Figure 15. Data are normalized to saline controls and are presented as Mean ± SEM.

The effect of cumulative increasing doses of solifenacin (n=4), gabapentin (n=11) and their matched combinations (e.g. Dose 1 for the combination was 10 mg/kg gabapentin and 3 mg/kg solifenacin; n=12) on bladder capacity (normalized to % Irritation Control) is depicted in Figure 16. Data are presented as Mean ± SEM. Note that the combination of drugs produced a greater than additive effect at the Low ($P<0.05$) and High doses ($P<0.05$) on reduction in bladder capacity caused by continuous intravesical exposure to dilute acetic acid. Synergy is also suggested by significant differences between Additive and Combination effects by 2-Way ANOVA ($P<0.0022$).

The ability of an $\alpha_2\delta$ subunit calcium channel modulator in combination with a smooth muscle modulator to produce a dramatic reversal in acetic acid irritation-induced reduction in bladder capacity strongly indicates efficacy in mammalian forms of painful and non-painful lower urinary tract disorders and associated irritative symptoms in normal and spinal cord injured patients. Furthermore, the combination of an $\alpha_2\delta$ subunit calcium channel modulator and a smooth muscle modulator produced a synergistic effect that was greater than what would be expected if the effects were simply additive.

Example 8 – Dilute Acetic Acid Model in Cats: Gabapentin and Oxybutynin

Objective and Rationale

The objective of this study was to determine the ability of an $\alpha_2\delta$ subunit calcium channel modulator in combination with a smooth muscle modulator to reverse the reduction in bladder capacity seen following continuous infusion of dilute acetic acid in a cat model, a commonly used model of overactive bladder. In particular, the current study utilized gabapentin as an exemplary $\alpha_2\delta$ subunit calcium channel modulator, and oxybutynin as an exemplary a smooth muscle modulator.

Materials and Methods

Alpha-chloralose anesthetized (50-100 mg/kg) normal female cats (2.5-3.5 kg; Harlan) were utilized in this study. Groups of cats were treated with oxybutynin

alone (n=5), gabapentin alone (n=5), and selected dose-matched combinations of oxybutynin and gabapentin (n=6).

Drugs and Preparation

Drugs were dissolved in normal saline at 0.01, 0.03, 0.1, 0.3, 1.0, 3.0 and 10mg/ml for oxybutynin and 3.0, 10, 30, 100 and 300 mg/ml for gabapentin. Combinations paired 0.1 mg/kg oxybutynin and 3 mg/kg gabapentin (Low), 0.3 mg/kg oxybutynin and 10 mg/kg gabapentin (Mid), and 1.0 mg/kg oxybutynin and 30 mg/kg gabapentin (High). Animals were dosed by volume of injection = body weight in kg.

Acute Anesthetized In Vivo Model

Female cats (2.5-3.5 kg; Harlan) had their food removed the night before the experiment. The following morning, the cat was anesthetized with isoflurane and prepped for surgery using aseptic technique. Polyethylene catheters were surgically placed to permit the measurement of bladder pressure, urethral pressure, arterial pressure, respiratory rate as well as for the delivery of drugs. Fine wire electrodes were implanted alongside the external urethral anal sphincter. Following surgery, the cats were slowly switched from the gas anesthetic isoflurane (2-3.5%) to alpha-chloralose (50-100 mg/kg). During control cystometry, saline was slowly infused into the bladder (0.5-1.0 ml/min) for 1 hour. The control cystometry was followed by 0.5% acetic acid in saline for the duration of the experiment. After assessing the cystometric variables under these baseline conditions, the effects of test drug(s) on micturition were determined via a 3-5 point dose response protocols.

Data Analysis

For the purposes of assessing synergy using all of the data simultaneously, bladder capacity data for each animal were normalized to % Recovery from Irritation, and this index was used as the measure of efficacy. Data from the experiments in which each of the drugs were administered alone were utilized to create theoretical populations of additive effects for each dose (low, mid and high) and these were compared by one-tailed t-test (individual dose comparisons) and by 2-Way ANOVA (across doses) to the actual combination drug data. For these purposes, the means and

standard deviations of each individual treatment's "dose-matched" (low, middle, and high) responses were added together to estimate the mean and standard deviation of the theoretical additive populations for which to compare to the actual data obtained from the combination experiments. The theoretical additive effect population $N = (N_{antimuscarinic} + N_{\alpha 2\delta\ subunit\ modulator}) - 1$. Because gabapentin alone was not tested at the 3.0 and the 10.0 mg.kg doses, and because there was no significant effect for gabapentin for the 30 mg/kg dose alone, the response at 30 mg/kg was used as a surrogate for the 3.0 and 10.0 mg/kg response in order to calculate the theoretical additive polulation. $P<0.050$ was considered significant. Additionally, % Voiding Efficiency was determined by the following formula: (Voided Volume / (Voided + Residual Volume)) * 100 for oxybutynin alone, gabapentin alone and the combination.

Results and Conclusions

The effect of cumulative increasing doses of oxybutynin (n=5), gabapentin (n=5) and their matched combinations (n=6) on bladder capacity is depicted in Figure 17. Data are normalized to saline controls and are presented as Mean ± SEM.

The theoretical additive effect of cumulative increasing doses of oxybutynin (n=5) and gabapentin (n=5), and their matched combinations (e.g. Dose 1 for the combination was 3 mg/kg gabapentin and 0.1 mg/kg oxybutynin; n=6) on bladder capacity (normalized to % Recovery from Irritation) is depicted in Figure 18. Data are presented as Mean ± SEM. Note that the combination of drugs produced a greater than additive effect at the Mid doses ($P=0.0490$) on reduction in bladder capacity caused by continuous intravesical exposure to dilute acetic acid.

The effect of cumulative increasing doses of oxybutynin (n=5), gabapentin (n=5) on voiding efficiency is depicted in Figure 19 (oxybutynin in Figure 19A, gabapentin in Figure 19B). Note the dose-dependent decrease in voiding efficiency caused by oxybutynin. Also note that gabapentin has no effect.

The effect of cumulative increasing doses of oxybutynin and gabapentin in combination (n=6) on voiding efficiency is depicted in Figure 20. Note that the dose-dependent decrease in voiding efficiency caused by oxybutynin is virtually prevented by co-administration of gabapentin.

At the highest oxybutynin (1 mg/kg) and gabapentin (30 mg/kg) dose combination tested in the cat, voiding efficiency was decreased only 16.7%. This is in striking contrast to the effect of oxybutynin alone at the same dose, which resulted in an 78.4% decrease in voiding efficiency. It is concluded that the addition of gabapentin (which alone at this dose caused a 10.1% increase in voiding efficiency) counteracts the undesirable negative effects of oxybutynin on voiding efficiency while simultaneously providing a positive and desirable synergistic effect on increasing bladder capacity.

The ability of an $\alpha_2\delta$ subunit calcium channel modulator in combination with a smooth muscle modulator to produce a dramatic reversal in acetic acid irritation-induced reduction in bladder capacity strongly indicates efficacy in mammalian forms of painful and non-painful lower urinary tract disorders and associated irritative symptoms in normal and spinal cord injured patients. Furthermore, the combination of an $\alpha_2\delta$ subunit calcium channel modulator and a smooth muscle modulator produced a synergistic effect that was greater than what would be expected if the effects were simply additive. In addition, the ability of an $\alpha_2\delta$ subunit calcium channel modulator to counteract negative side effects of a smooth muscle modulator while simultaneously producing a synergistic positive effect on bladder overactivity strongly suggests efficacy in relieving the irritative symptoms without compromising voiding capability in bladder outlet obstructed patients, such as those suffering from benign prostatic hyperplasia and associated irritative symptoms.

Example 9 – Spinal Cord Injury Model: Gabapentin and Oxybutynin

Objective and Rationale

The objective of this study was to determine the ability of an $\alpha_2\delta$ subunit calcium channel modulator in combination with a smooth muscle modulator on the ability to increase bladder capacity in spinal cord injured (SCI) rats, a commonly used model of neurogenic bladder. In particular, the current study utilized gabapentin as an exemplary $\alpha_2\delta$ subunit calcium channel modulator, and oxybutynin as an exemplary a smooth muscle modulator.

Materials and Methods

Awake restrained SCI female rats were treated with combinations of oxybutynin and gabapentin (n=3). Cumulative dose-response protocols were utilized with half log increments for all studies.

Drugs and Preparation

Drugs were dissolved in normal saline at 1, 3 and 10 mg/ml for oxybutynin and 30, 100 and 300 mg/ml for gabapentin. In these studies, combinations may be subsequently referred to as Low, Mid and High.

Awake Restrained SCI In Vivo Model

Animal Preparation: Female rats (250-300 g body weight) were anesthetized with 4% isofluorane (2% maintenance) and a laminectomy was performed at the T9-10 spinal level. The spinal cord was completely transected, and the wound was closed in layers. The animals received antibiotic (100 mg/kg ampicillin) immediately thereafter and every third day during recovery until the day of terminal experimentation. SCI rats had their bladders manually expressed twice daily by external crede, and were maintained in single housing for 2-3 weeks until evidence of recovery of voiding function was seen. On the day of the experiment, the animals were anesthetized with 4% isofluorane (2% maintenance) and a saline-filled catheter (PE-50) was inserted into the jugular vein for intravenous drug administration. This catheter was exited via the midscapular region and the ventral wound was closed with silk. Via a midline lower abdominal incision, a flared-tipped PE 50 catheter was inserted into the bladder dome for bladder filling and pressure recording. The abdominal cavity was closed in layers, with the bladder catheter exiting at the apex of the wound. Fine silver or stainless steel wire electrodes were inserted into the external urethral sphincter (EUS) percutaneously for electromyography (EMG). The animal was mounted in a Ballman restraint cage and allowed to recover from anesthesia for 1 hour prior to collection of control data.

Experimental Design: Saline was continuously infused at a rate of 0.100 ml/min via the bladder-filling catheter for 60 minutes to obtain a baseline of lower

urinary tract activity (continuous cystometry; CMG). Following the control period, 3 vehicle injections were made at 20 minute intervals to determine vehicle effects, if any. Subsequently, increasing doses of a selected active agent, or combination of agents, at half log increments were administered intravenously at 30 minute intervals in order to construct a cumulative dose-response relationship. At the end of the control cystometry period, the third vehicle (Veh 3), and 20 minutes following each subsequent treatment, the infusion pump was stopped, the bladder was emptied by fluid withdrawal via the infusion catheter and a single filling cystometrogram was performed at the same flow rate in order to determine changes in bladder capacity, as determined by a voiding contraction, caused by the intravenous drug administration.

Data Analysis

Bladder capacity data for each animal was normalized to % Veh 3, and data were analyzed using a non-parametric repeated measures 1-Way ANOVA (Friedman Test) with the Dunn's Multiple Comparison Post-test. $P<0.05$ was considered significant.

Results and Conclusions

The effect of cumulative increasing doses of the combination of oxybutynin and gabapentin (e.g. Dose 1 for the combination was 30 mg/kg gabapentin and 1 mg/kg oxybutynin; n=3) on bladder capacity in chronic SCI rats is depicted in Figure 21. Note the marked dose-dependent increase in bladder capacity ($P=0.0278$). Data are normalized to vehicle controls and are presented as Mean ± SEM.

The effect of cumulative increasing doses of the combination of oxybutynin and gabapentin (n=3) on bladder instability, as measured by a significant decrease in the number of non-voiding contractions greater than 8 cm H_2O ($P=0.0174$), is depicted in Figure 22. Data are presented as Mean ± SEM.

The effect of cumulative increasing doses of the combination of oxybutynin and gabapentin (n=3) on bladder instability, as measured by the significant increase in latency to the appearance of non-voiding contractions ($P=0.0017$), is depicted in Figure 23. Data are presented as Mean ± SEM.

The combination of an $\alpha_2\delta$ subunit calcium channel modulator and a smooth muscle modulator was capable of nearly doubling bladder capacity and significantly

reduced bladder instability in a rat model of neurogenic bladder. This finding stands in contrast to the effects of vanilloid agents, such as capsaicin, which have been shown to reduce bladder instability in SCI rats, but not effect bladder capacity to voiding (Cheng *et al.*, 1995, *Brain Res.* 678:40-48). Because both spinal cord injury and benign prostatic hyperplasia are characterized by outlet obstruction, bladder hypertrophy and bladder instability, these findings strongly indicate efficacy for both spinal cord injury and benign prostatic hyperplasia, including irritative symptoms and/or obstructive symptoms associated with benign prostatic hyperplasia.

All publications and patent applications mentioned in the specification are indicative of the level of those skilled in the art to which this invention pertains. All publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

CLAIMS

What is claimed is:

1. A method for treating a lower urinary tract disorder characterized by having at least one symptom selected from the group consisting of urinary frequency, urinary urgency, and nocturia, which comprises administering to an individual in need thereof a therapeutically effective amount of a first component that is an $\alpha_2\delta$ subunit calcium channel modulator, in combination with a second component that is a smooth muscle modulator.

2. The method of claim 1, wherein said first component and said second component are contained within a single pharmaceutical formulation.

3. The method of claim 1, wherein said first component and said second component are contained within separate pharmaceutical formulations.

4. The method of claim 3, wherein said first component and said second component are administered concurrently.

5. The method of claim 3, wherein said first component and said second component are administered sequentially.

6. The method of claim 1, wherein the $\alpha_2\delta$ subunit calcium channel modulator is a GABA analog.

7. The method of claim 6, wherein the GABA analog is Gabapentin or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof.

8. The method of claim 6, wherein the GABA analog is Pregabalin or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof.

9. The method of claim 1, wherein said smooth muscle modulator is selected from the group consisting of: antimuscarinics, β3 adrenergic agonists, spasmolytics, neurokinin receptor antagonists, bradykinin receptor antagonists, and nitric oxide donors.

10. The method of claim 9, wherein said smooth muscle modulator is an antimuscarinic.

11. The method of claim 10, wherein the antimuscarinic is Oxybutynin or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof.

12. The method of claim 10, wherein the antimuscarinic is Tolterodine or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof.

13. The method of claim 10, wherein the antimuscarinic is Propiverine or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof.

14. The method of claim 10, wherein the antimuscarinic is Solifenacin monohydrochloride or an acid, salt, enantiomer, analog, ester, amide, prodrug, active metabolite, or derivative thereof.

15. The method of claim 1, wherein said $\alpha_2\delta$ subunit calcium channel modulator is Gabapentin or acids, salts, enantiomers, analogs, esters, amides, prodrugs, active metabolites, and derivatives thereof, and wherein said smooth muscle modulator is Oxybutynin or acids, salts, enantiomers, analogs, esters, amides, prodrugs, active metabolites, and derivatives thereof.

16. The method of claim 1, wherein said $\alpha_2\delta$ subunit calcium channel modulator is Pregabalin or acids, salts, enantiomers, analogs, esters, amides, prodrugs, active metabolites, and derivatives thereof, and wherein said smooth muscle

modulator is Oxybutynin or acids, salts, enantiomers, analogs, esters, amides, prodrugs, active metabolites, and derivatives thereof.

17. The method of claim 1, wherein said first component and said second component are administered on an as-needed basis.

18. The method of claim 1, wherein said first component and said second component are administered prior to commencement of an activity wherein suppression of the symptoms of a lower urinary tract disorder would be desirable.

19. The method of claim 18, wherein said first component and said second component are administered from about 0 to about 3 hours prior to commencement of an activity wherein suppression of said symptoms would be desirable.

20. The method of claim 1, wherein said first component and said second component are administered orally, transmucosally, sublingually, buccally, intranasally, transurethrally, rectally, by inhalation, topically, transdermally, parenterally, intrathecally, vaginally, or perivaginally.

21. The method of claim 1, wherein said first component and said second component are administered to treat overactive bladder or the irritative or obstructive symptoms of benign prostatic hyperplasia.

22. The method of claim 1, wherein said first component and said second component are administered to treat urinary frequency.

23. The method of claim 1, wherein said first component and said second component are administered to treat urinary urgency.

24. The method of claim 1, wherein said first component and said second component are administered to treat nocturia.

25. The method of claim 1, wherein at least one detrimental side effect associated with single administration of said first component or single administration of said second component is lessened by concurrent administration of said first component and said second component.

26. The method of claim 25 wherein said first component and said second component are administered to treat overactive bladder or the irritative or obstructive symptoms of benign prostatic hyperplasia.

27. A method for treating a lower urinary tract disorder characterized by having at least one symptom selected from the group consisting of urinary frequency, urinary urgency, and nocturia, comprising administering to an individual in need thereof a therapeutically effective amount of at least one component selected from an $\alpha_2\delta$ subunit calcium channel modulator and a smooth muscle modulator.

28. A pharmaceutical composition comprising a first component that is an $\alpha_2\delta$ subunit calcium channel modulator, in combination with a second component that is a smooth muscle modulator, wherein said first component and said second component are in amounts sufficient to treat a lower urinary tract disorder characterized by having at least one symptom selected from the group consisting of urinary frequency, urinary urgency, and nocturia.

29. A pharmaceutical composition comprising a first component that is Gabapentin or pharmaceutically acceptable acids, salts, esters, amides, prodrugs, or active metabolites thereof, in combination with a second component that is Oxybutynin or pharmaceutically acceptable acids, salts, esters, amides, prodrugs, or active metabolites thereof, wherein said first component and said second component are in amounts sufficient to treat a lower urinary tract disorder characterized by having at least one symptom selected from the group consisting of urinary frequency, urinary urgency, and nocturia.

30. The pharmaceutical composition of claim 29 wherein said first component is present in an amount from about 50 mg to about 2400 mg, and wherein said second component is present in an amount equal to or less than about 5 mg.

31. The pharmaceutical composition of claim 30 wherein said first component is in an amount of about 200 mg.

32. The pharmaceutical composition of claim 30 wherein said second component is in an amount of about 2.5 mg.

33. The pharmaceutical composition of claim 30 wherein said second component is in an amount of about 1.25 mg.

34. A pharmaceutical composition comprising a first component that is Pregabalin or pharmaceutically acceptable acids, salts, esters, amides, prodrugs, or active metabolites thereof, in combination with a second component that is Oxybutynin or pharmaceutically acceptable acids, salts, esters, amides, prodrugs, or active metabolites thereof, wherein said first component and said second component are in amounts sufficient to treat a lower urinary tract disorder characterized by having at least one symptom selected from the group consisting of urinary frequency, urinary urgency, and nocturia.

35. A pharmaceutical composition for the treatment of a lower urinary tract disorder characterized by having at least one symptom selected from the group consisting of urinary frequency, urinary urgency, and nocturia, comprising a first component that is Gabapentin or pharmaceutically acceptable acids, salts, esters, amides, prodrugs, or active metabolites thereof, in combination with a second component that is Oxybutynin or pharmaceutically acceptable acids, salts, esters, amides, prodrugs, or active metabolites thereof, wherein said first component and said second component are present in a ratio from about 1:1 to about 800:1 or from about 1:1 to about 1:800, respectively, based on a fraction of their respective ED_{50} values.

36. A combination for the treatment of a lower urinary tract disorder characterized by having at least one symptom selected from the group consisting of urinary frequency, urinary urgency, and nocturia, comprising a first component that is Gabapentin or pharmaceutically acceptable acids, salts, esters, amides, prodrugs, or active metabolites thereof, in combination with a second component that is Oxybutynin or pharmaceutically acceptable acids, salts, esters, amides, prodrugs, or active metabolites thereof, wherein said first component and said second component are in a weight/weight ratio of from 1:1 to about 800:1 or from about 1:1 to about 1:800, respectively.

37. A pharmaceutical composition comprising Oxybutynin, wherein said Oxybutynin is in an amount less than about 2.5 mg.

38. A packaged kit for a patient to use in the treatment of a lower urinary tract disorder characterized by having at least one symptom selected from the group consisting of urinary frequency, urinary urgency, and nocturia, comprising: at least one component selected from an $\alpha_2\delta$ subunit calcium channel modulator and a smooth muscle modulator; a container housing said component or components during storage and prior to administration; and instructions for carrying out drug administration of an $\alpha_2\delta$ subunit calcium channel modulator with a smooth muscle modulator in a manner effective to treat said lower urinary tract disorder.

39. The packaged kit of claim 38 wherein said first component and said second component are contained in the same pharmaceutical formulation.

40. The packaged kit of claim 39 wherein said first component is Gabapentin or pharmaceutically acceptable acids, salts, esters, amides, prodrugs, or active metabolites thereof, and wherein said second component is Oxybutynin or pharmaceutically acceptable acids, salts, esters, amides, prodrugs, or active metabolites thereof.

41. The packaged kit of claim 38 wherein said first component and said second component are contained in separate pharmaceutical formulations.

42. The packaged kit of claim 41 wherein said instructions include directions for carrying out drug administration of said first component and said second component sequentially or concurrently.

43. The packaged kit of claim 42 wherein said first component is Gabapentin or pharmaceutically acceptable acids, salts, esters, amides, prodrugs, or active metabolites thereof, and wherein said second component is Oxybutynin or pharmaceutically acceptable acids, salts, esters, amides, prodrugs, or active metabolites thereof.

AMENDED CLAIMS

[Received by the International Bureau on 20 September 2004 (20.09.2004): original claims 1-43 replaced by amended claims, 1-51 (8 pages)]

What is claimed is:

1. A method for treating a symptom of a lower urinary tract disorder, comprising:

(a) administering an $\alpha_2\delta$ subunit calcium channel modulator selected from the group consisting of Gabapentin and Pregabalin; and

(b) administering an antimuscarinic selected from the group consisting of Oxybutynin, Tolterodine, Propiverine, and Solifenacin monohydrochloride;

wherein said $\alpha_2\delta$ subunit calcium channel modulator and said antimuscarinic are in therapeutically effective amounts sufficient to treat a symptom of a lower urinary tract disorder.

2. The method of claim 1, wherein said $\alpha_2\delta$ subunit calcium channel modulator and said antimuscarinic are contained within a single pharmaceutical formulation.

3. The method of claim 1, wherein said $\alpha_2\delta$ subunit calcium channel modulator and said antimuscarinic are contained within separate pharmaceutical formulations.

4. The method of claim 3, wherein said $\alpha_2\delta$ subunit calcium channel modulator and said antimuscarinic are administered concurrently.

5. The method of claim 3, wherein said $\alpha_2\delta$ subunit calcium channel modulator and said antimuscarinic are administered sequentially.

6. The method of claim 1, wherein said $\alpha_2\delta$ subunit calcium channel modulator and said antimuscarinic are administered on an as-needed basis.

7. The method of claim 1, wherein said $\alpha_2\delta$ subunit calcium channel modulator and said antimuscarinic are administered prior to commencement of an activity wherein suppression of the symptoms of a lower urinary tract disorder would be desirable.

8. The method of claim 7, wherein said $\alpha_2\delta$ subunit calcium channel modulator and said antimuscarinic are administered from about 0 to about 3 hours prior to commencement of an activity wherein suppression of said symptoms would be desirable.

9. The method of claim 1, wherein said $\alpha_2\delta$ subunit calcium channel modulator and said antimuscarinic are administered orally, transmucosally, sublingually, buccally, intranasally, transurethrally, rectally, by inhalation, topically, transdermally, parenterally, intrathecally, vaginally, or perivaginally.

10. The method of claim 1, wherein the symptom of a lower urinary tract disorder is associated with benign prostatic hyperplasia or overactive bladder.

11. The method of claim 1, wherein the symptom of a lower urinary tract disorder is urinary frequency.

12. The method of claim 1, wherein the symptom of a lower urinary tract disorder is urinary urgency.

13. The method of claim 1, wherein the symptom of a lower urinary tract disorder is nocturia.

14. The method of claim 1, wherein the symptom of a lower urinary tract disorder is incontinence.

15. The method of claim 1 wherein at least one detrimental side effect associated with single administration of said $\alpha_2\delta$ subunit calcium channel modulator

or single administration of said antimuscarinic is lessened by concurrent administration of said $\alpha_2\delta$ subunit calcium channel modulator and said antimuscarinic.

16. The method of claim 1, wherein said $\alpha_2\delta$ subunit calcium channel modulator is Gabapentin and wherein said antimuscarinic is Oxybutynin.

17. The method of claim 1, wherein said $\alpha_2\delta$ subunit calcium channel modulator is Gabapentin and wherein said antimuscarinic is Tolterodine.

18. The method of claim 1, wherein said $\alpha_2\delta$ subunit calcium channel modulator is Gabapentin and wherein said antimuscarinic is Propiverine.

19. The method of claim 1, wherein said $\alpha_2\delta$ subunit calcium channel modulator is Gabapentin and wherein said antimuscarinic is Solifenacin monohydrochloride.

20. The method of claim 1, wherein said $\alpha_2\delta$ subunit calcium channel modulator is Pregabalin and wherein said antimuscarinic is Oxybutynin.

21. The method of claim 1, wherein said $\alpha_2\delta$ subunit calcium channel modulator is Pregabalin and wherein said antimuscarinic is Tolterodine.

22. The method of claim 1, wherein said $\alpha_2\delta$ subunit calcium channel modulator is Pregabalin and wherein said antimuscarinic is Propiverine.

23. The method of claim 1, wherein said $\alpha_2\delta$ subunit calcium channel modulator is Pregabalin and wherein said antimuscarinic is Solifenacin monohydrochloride.

24. A pharmaceutical composition comprising:

(a) an $\alpha_2\delta$ subunit calcium channel modulator selected from the group consisting of Gabapentin and Pregabalin; and

(b) an antimuscarinic selected from the group consisting of Oxybutynin, Tolterodine, Propiverine, and Solifenacin monohydrochloride; and wherein said $\alpha_2\delta$ subunit calcium channel modulator and said antimuscarinic are in therapeutically effective amounts sufficient to treat a symptom of a lower urinary tract disorder.

25. The pharmaceutical composition of claim 24 wherein said $\alpha_2\delta$ subunit calcium channel modulator is present in an amount from about 50 mg to about 2400 mg, and wherein said antimuscarinic is present in an amount equal to or less than about 5 mg.

26. The pharmaceutical composition of claim 24 wherein said $\alpha_2\delta$ subunit calcium channel modulator is in an amount of about 200 mg.

27. The pharmaceutical composition of claim 24 wherein said antimuscarinic is in an amount of about 2.5 mg.

28. The pharmaceutical composition of claim 24 wherein said antimuscarinic is in an amount of about 1.25 mg.

29. The pharmaceutical composition of claim 24 wherein said $\alpha_2\delta$ subunit calcium channel modulator and said antimuscarinic are present in a ratio from about 1:1 to about 800:1 or from about 1:1 to about 1:800, respectively, based on a fraction of their respective ED_{50} values.

30. The pharmaceutical composition of claim 24 wherein said $\alpha_2\delta$ subunit calcium channel modulator and said antimuscarinic are in a weight/weight ratio of from 1:1 to about 800:1 or from about 1:1 to about 1:800, respectively.

31. The pharmaceutical composition of claim 24, wherein said $\alpha_2\delta$ subunit calcium channel modulator and said antimuscarinic are formulated for oral,

transmucosal, sublingual, buccal, intranasal, transurethral, rectal, inhalation, topical, transdermal, parenteral, intrathecal, vaginal, or perivaginal administration.

32. The pharmaceutical composition of claim 24, wherein the symptom of a lower urinary tract disorder is associated with benign prostatic hyperplasia or overactive bladder.

33. The pharmaceutical composition of claim 24, wherein the symptom of a lower urinary tract disorder is urinary frequency.

34. The pharmaceutical composition of claim 24, wherein the symptom of a lower urinary tract disorder is urinary urgency.

35. The pharmaceutical composition of claim 24, wherein the symptom of a lower urinary tract disorder is nocturia.

36. The pharmaceutical composition of claim 24, wherein the symptom of a lower urinary tract disorder is incontinence.

37. The pharmaceutical composition of claim 24, wherein said $\alpha_2\delta$ subunit calcium channel modulator is Gabapentin and wherein said antimuscarinic is Oxybutynin.

38. The pharmaceutical composition of claim 24, wherein said $\alpha_2\delta$ subunit calcium channel modulator is Gabapentin and wherein said antimuscarinic is Tolterodine.

39. The pharmaceutical composition of claim 24, wherein said $\alpha_2\delta$ subunit calcium channel modulator is Gabapentin and wherein said antimuscarinic is Propiverine.

40. The pharmaceutical composition of claim 24, wherein said $\alpha_2\delta$ subunit calcium channel modulator is Gabapentin and wherein said antimuscarinic is Solifenacin monohydrochloride.

41. The pharmaceutical composition of claim 24, wherein said $\alpha_2\delta$ subunit calcium channel modulator is Pregabalin and wherein said antimuscarinic is Oxybutynin.

42. The pharmaceutical composition of claim 24, wherein said $\alpha_2\delta$ subunit calcium channel modulator is Pregabalin and wherein said antimuscarinic is Tolterodine.

43. The pharmaceutical composition of claim 24, wherein said $\alpha_2\delta$ subunit calcium channel modulator is Pregabalin and wherein said antimuscarinic is Propiverine.

44. The pharmaceutical composition of claim 24, wherein said $\alpha_2\delta$ subunit calcium channel modulator is Pregabalin and wherein said antimuscarinic is Solifenacin monohydrochloride.

45. A pharmaceutical composition comprising Oxybutynin, wherein said Oxybutynin is in an amount less than about 2.5 mg.

46. A packaged kit for use in the treatment of a symptom of a lower urinary tract disorder, comprising:

(a) an $\alpha_2\delta$ subunit calcium channel modulator selected from the group consisting of Gabapentin and Pregabalin;

(b) an antimuscarinic selected from the group consisting of Oxybutynin, Tolterodine, Propiverine, and Solifenacin monohydrochloride;

(c) a container housing said $\alpha_2\delta$ subunit calcium channel modulator and said antimuscarinic during storage and prior to administration; and

(d) instructions for carrying out drug administration of said $\alpha_2\delta$ subunit calcium channel modulator and said antimuscarinic in a manner effective to treat said symptom of a lower urinary tract disorder.

47. The packaged kit of claim 46 wherein said $\alpha_2\delta$ subunit calcium channel modulator and said antimuscarinic are contained in the same pharmaceutical formulation.

48. The packaged kit of claim 46 wherein said $\alpha_2\delta$ subunit calcium channel modulator and said antimuscarinic are contained in separate pharmaceutical formulations.

49. The packaged kit of claim 46 wherein said instructions include directions for carrying out drug administration of said $\alpha_2\delta$ subunit calcium channel modulator and said antimuscarinic sequentially or concurrently.

50. A packaged kit for use in the treatment of a symptom of a lower urinary tract disorder, comprising:

(a) an $\alpha_2\delta$ subunit calcium channel modulator selected from the group consisting of Gabapentin and Pregabalin;

(b) a container housing said $\alpha_2\delta$ subunit calcium channel modulator during storage and prior to administration; and

instructions for carrying out drug administration of said $\alpha_2\delta$ subunit calcium channel modulator sequentially or concurrently with an antimuscarinic selected from the group consisting of Oxybutynin, Tolterodine, Propiverine, and Solifenacin monohydrochloride, in a manner effective to treat said symptom of a lower urinary tract disorder.

51. A packaged kit for use in the treatment of a symptom of a lower urinary tract disorder, comprising:

(a) an antimuscarinic selected from the group consisting of Oxybutynin, Tolterodine, Propiverine, and Solifenacin monohydrochloride;

(b) a container housing said antimuscarinic during storage and prior to administration; and

instructions for carrying out drug administration of said antimuscarinic sequentially or concurrently with an $\alpha_2\delta$ subunit calcium channel modulator selected from the group consisting of Gabapentin and Pregabalin, in a manner effective to treat said symptom of a lower urinary tract disorder.

Figure 1

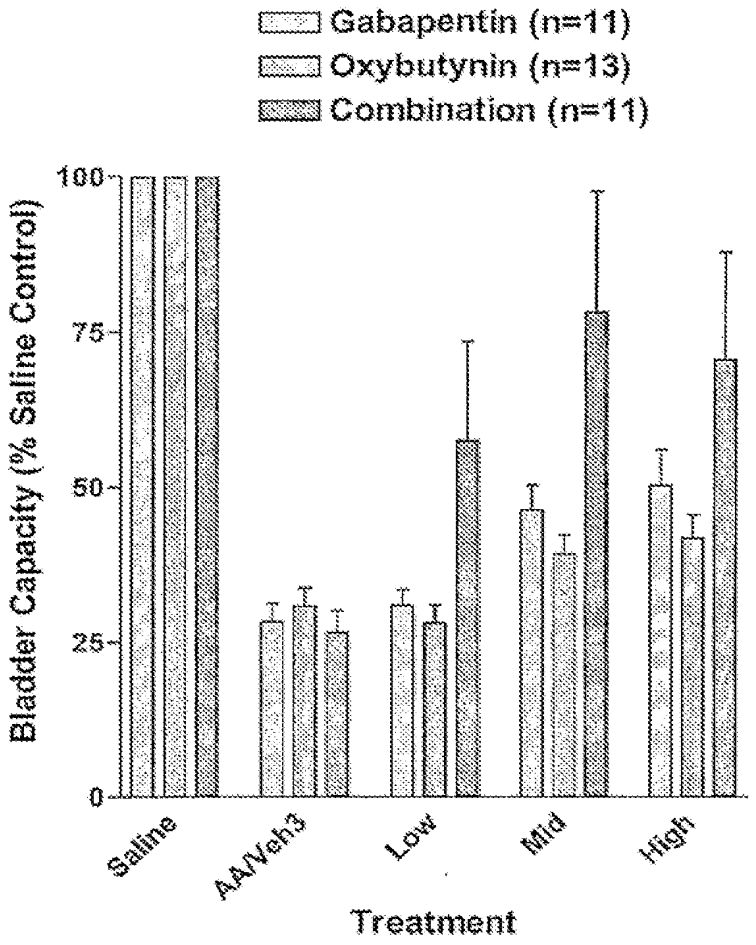
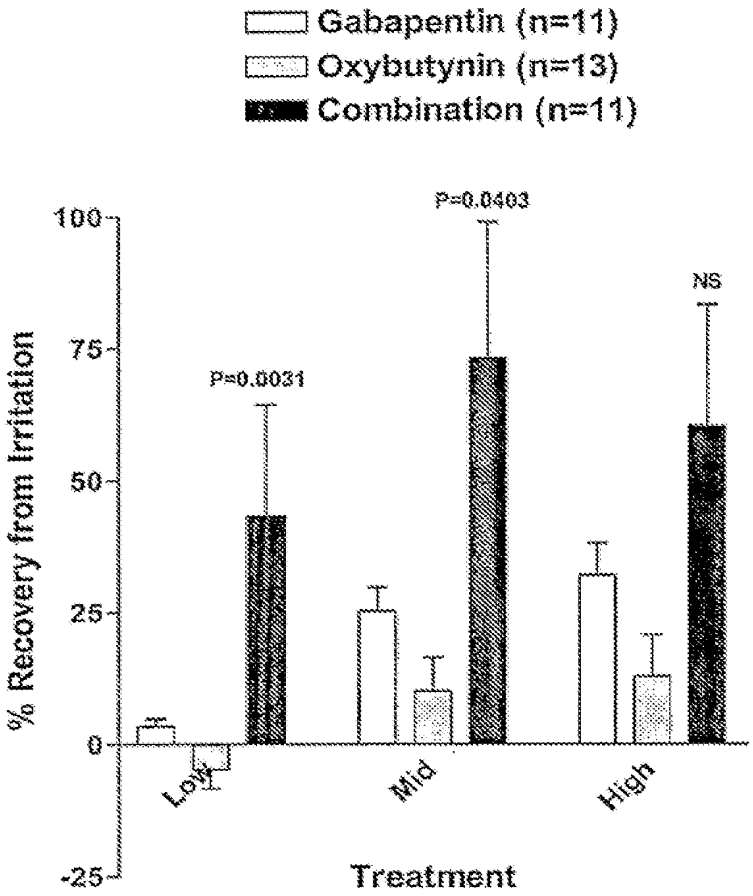

Gabapentin (n=11)
Oxybutynin (n=13)
Combination (n=11)
Bladder Capacity (% Saline Control)
100
75
50
25
0
Saline
AA/Veh3
Low
Mid
High
Treatment

Figure 2



P=0.0046 for Synergy by 2-Way ANOVA

Figure 3

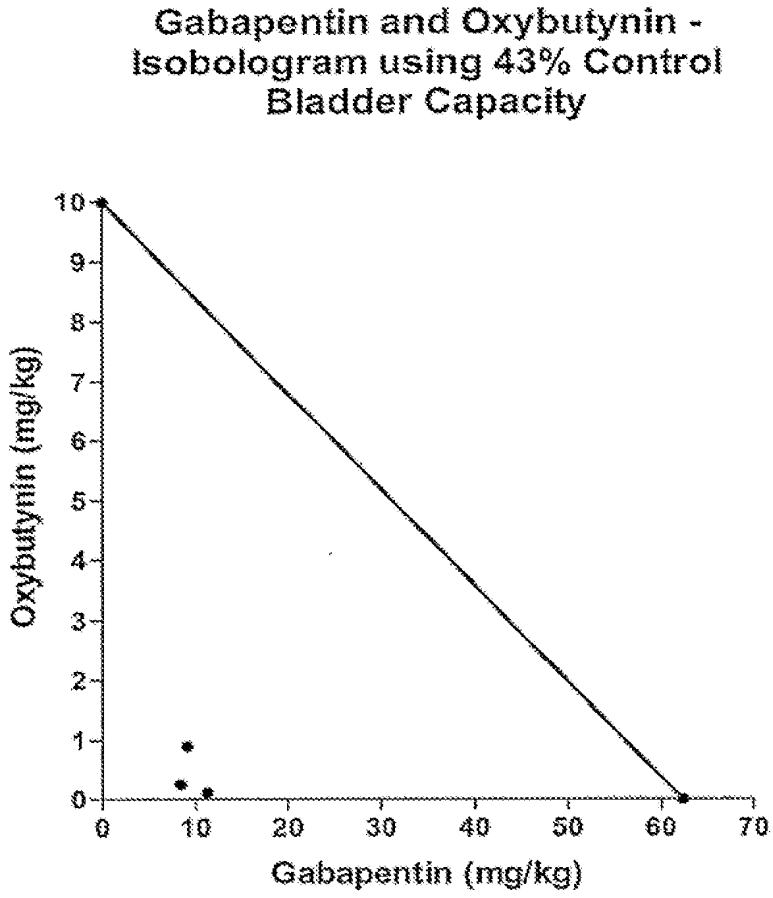

Gabapentin and Oxybutynin - Isobologram using 43% Control Bladder Capacity
Oxybutynin (mg/kg)
Gabapentin (mg/kg)
0
1
2
3
4
5
6
7
8
9
10
0
10
20
30
40
50
60
70

Figure 4

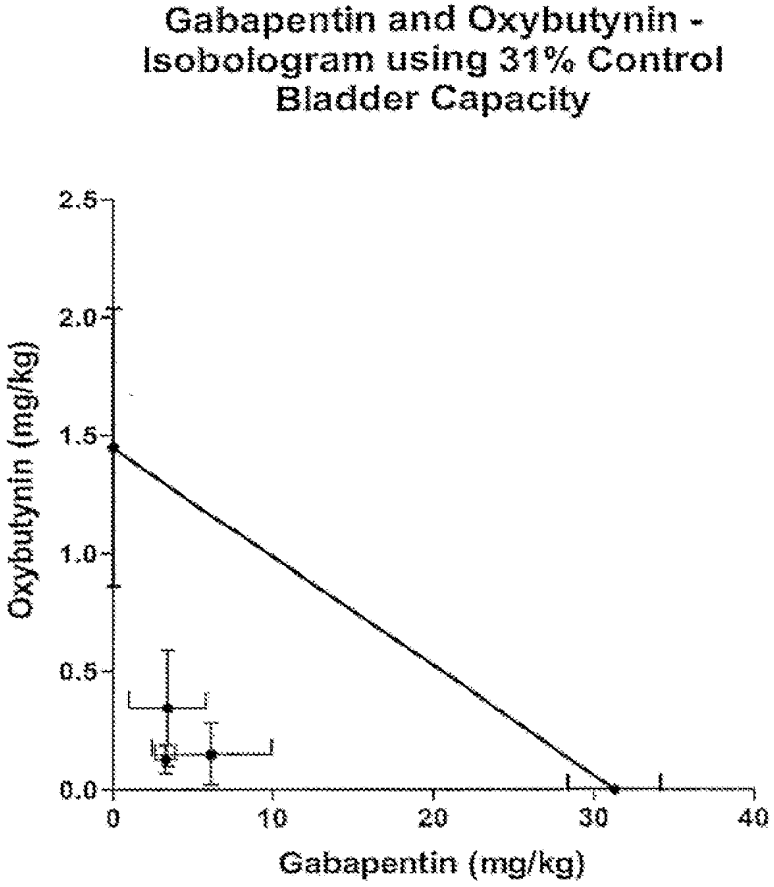

Gabapentin and Oxybutynin - Isobologram using 31% Control Bladder Capacity
Oxybutynin (mg/kg)
2.5
2.0
1.5
1.0
0.5
0.0
0
10
20
30
40
Gabapentin (mg/kg)

Figure 5

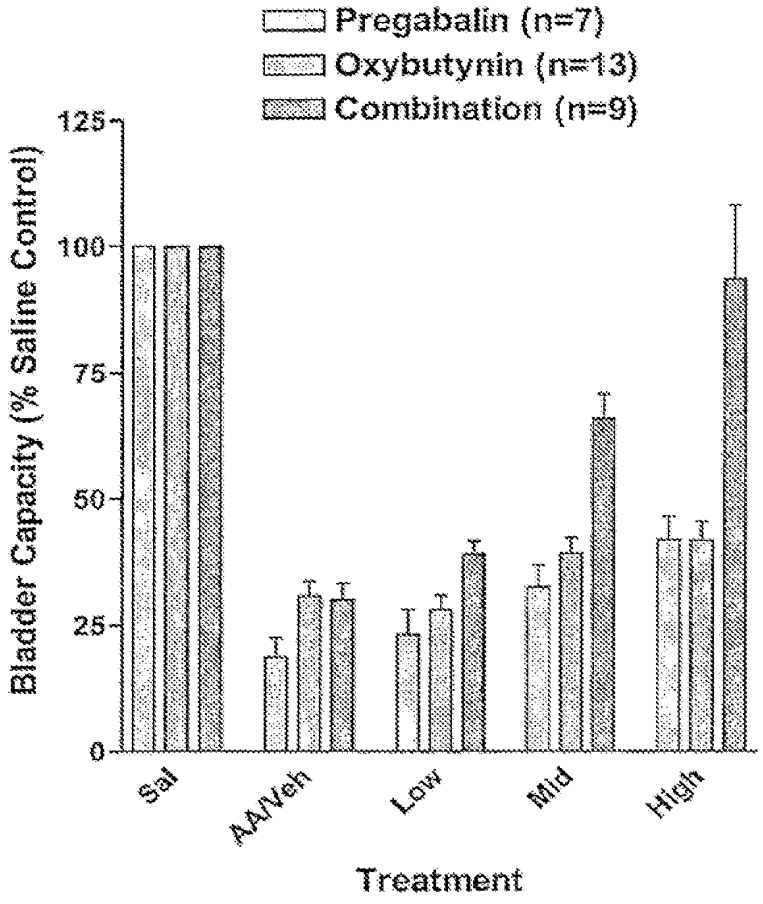

Pregabalin (n=7)
Oxybutynin (n=13)
Combination (n=9)
Bladder Capacity (% Saline Control)
125
100
75
50
25
0
Sal
AA/Veh
Low
Mid
High
Treatment

Figure 6

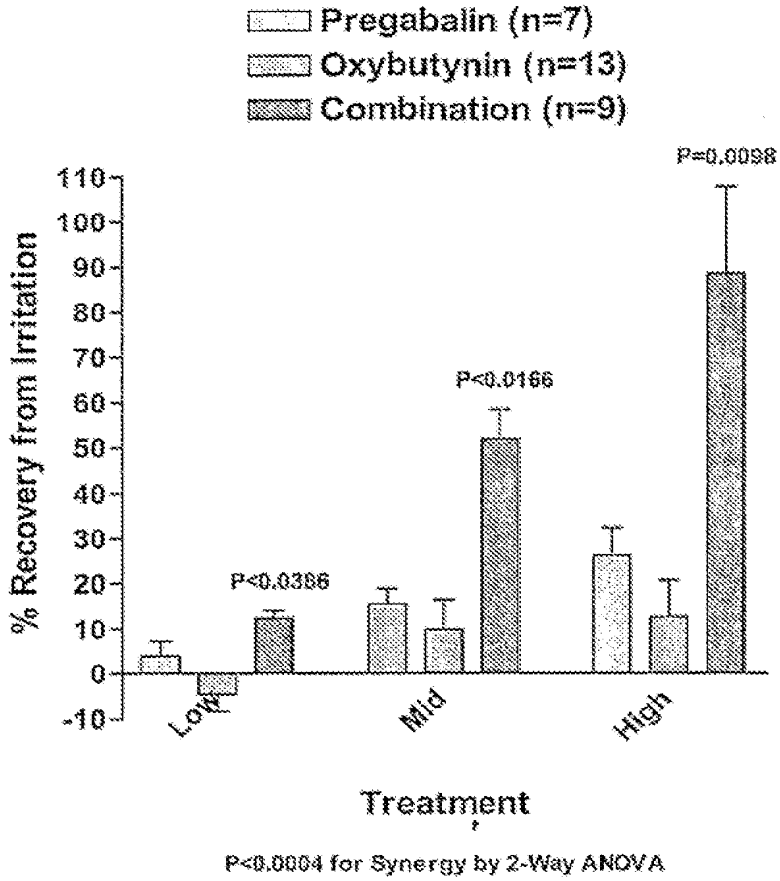

Pregabalin (n=7)
Oxybutynin (n=13)
Combination (n=9)
% Recovery from Irritation
110
100
90
80
70
60
50
40
30
20
10
0
-10
P=0.0098
P<0.0166
P<0.0386
Low
Mid
High
Treatment
P<0.0004 for Synergy by 2-Way ANOVA

Figure 7

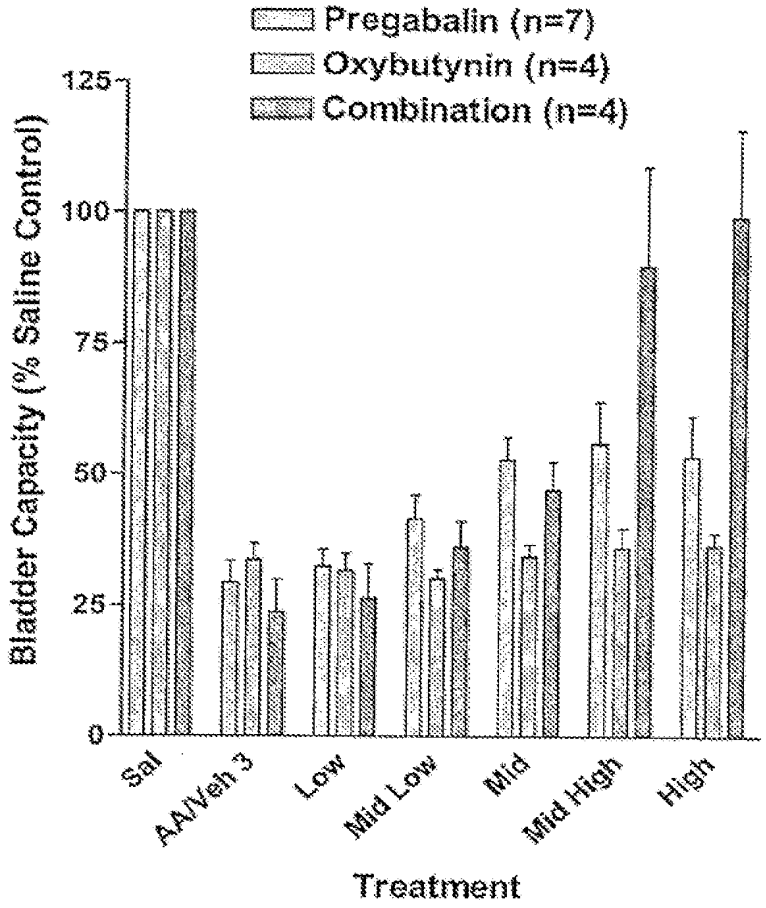
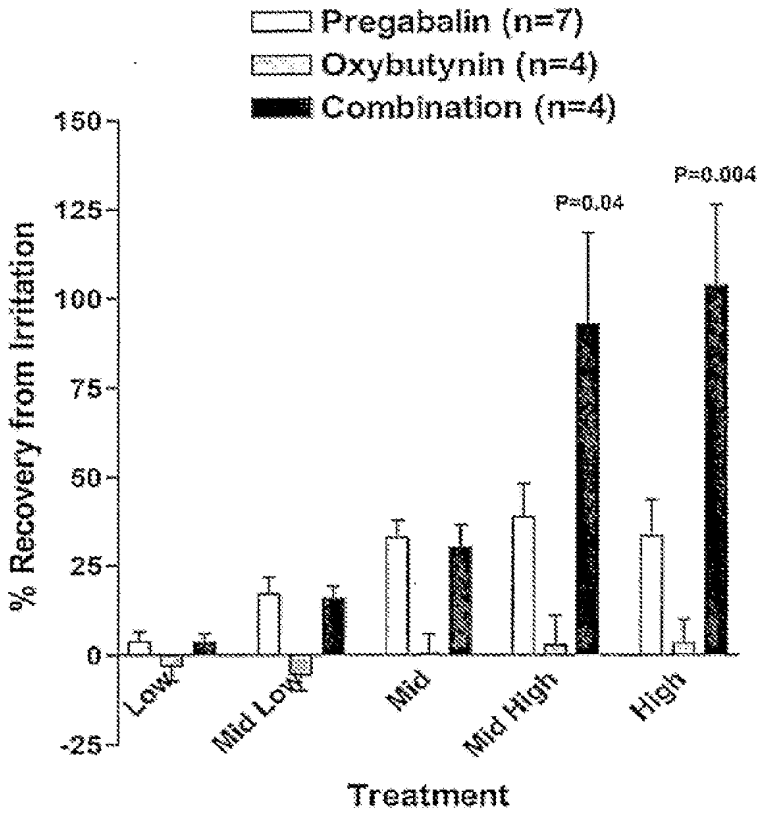

Pregabalin (n=7)
Oxybutynin (n=4)
Combination (n=4)
Bladder Capacity (% Saline Control)
125
100
75
50
25
0
Sal
AA/Veh 3
Low
Mid Low
Mid
Mid High
High
Treatment

Figure 8



P=0.0037 for Synergy by 2-Way ANOVA

Figure 9

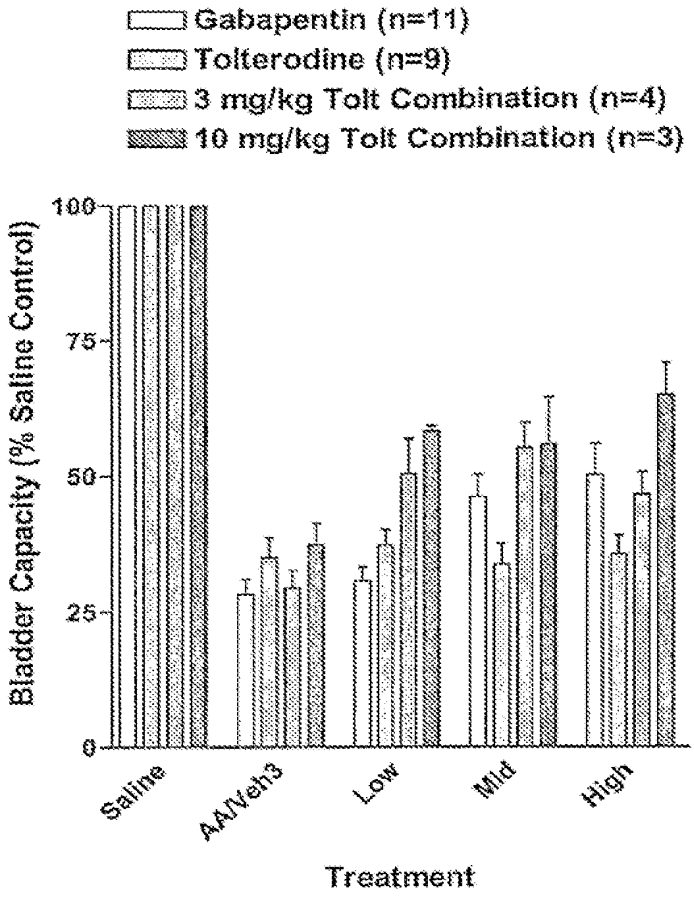
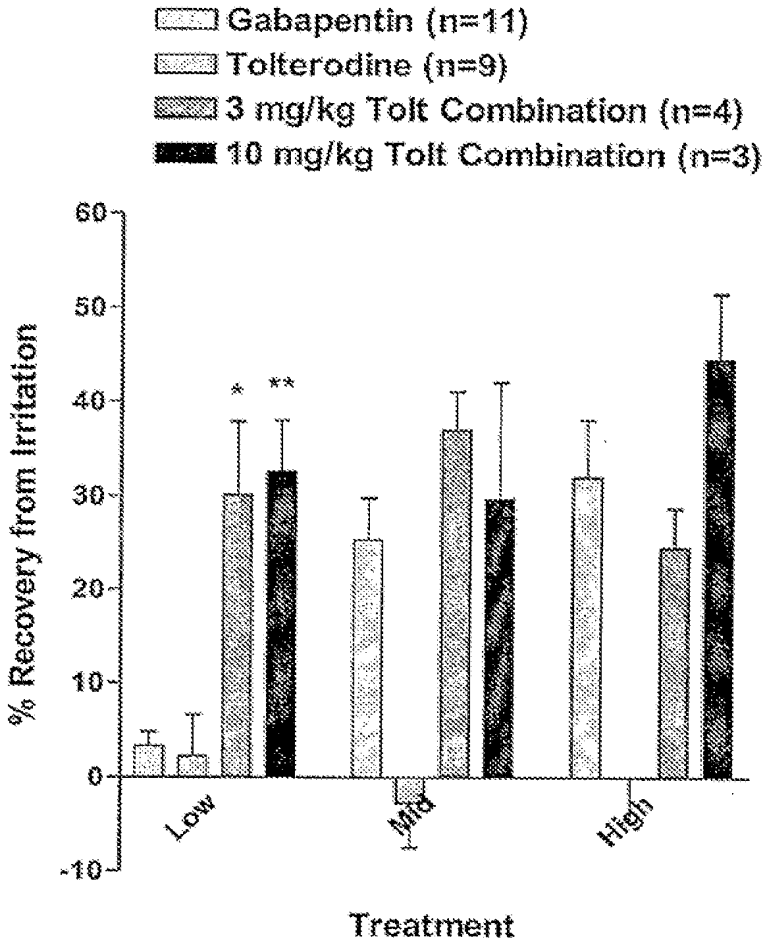

Gabapentin (n=11)
Tolterodine (n=9)
3 mg/kg Tolt Combination (n=4)
10 mg/kg Tolt Combination (n=3)
Bladder Capacity (% Saline Control)
100
75
50
25
0
Saline
AA/Veh3
Low
Mid
High
Treatment

Figure 10



*P=0.0099 for Synergy by t Test
**P=0.0104 for Synergy by t Test

Figure 11

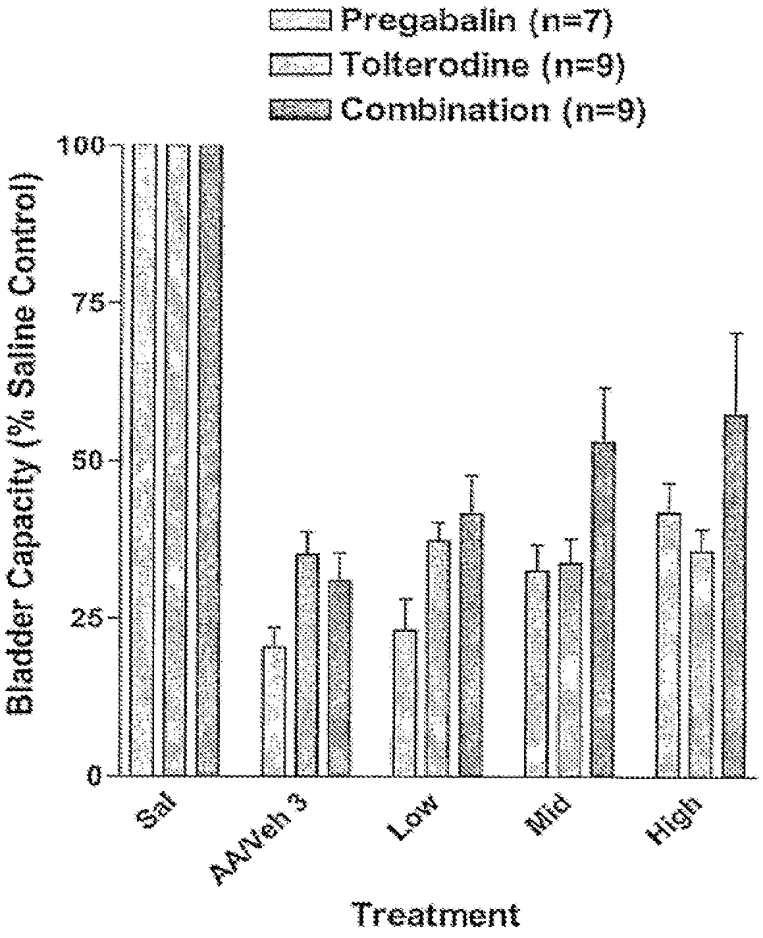
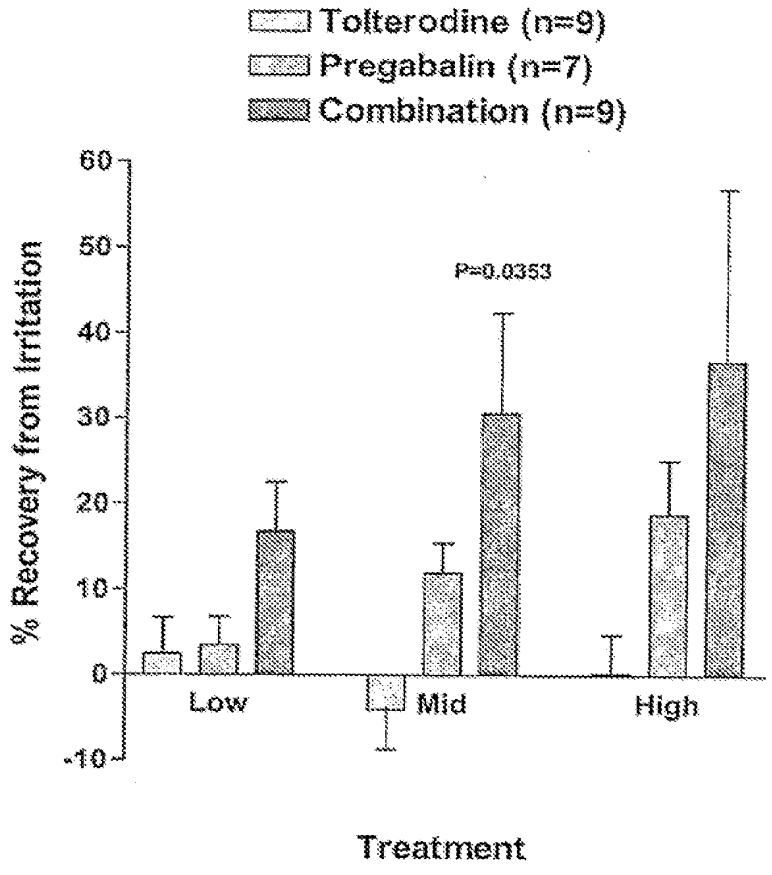

Pregabalin (n=7)
Tolterodine (n=9)
Combination (n=9)
Bladder Capacity (% Saline Control)
100
75
50
25
0
Sal
AA/Veh 3
Low
Mid
High
Treatment

Figure 12



P=0.0234 Additive vs. Combination by 2-Way ANOVA

Figure 13

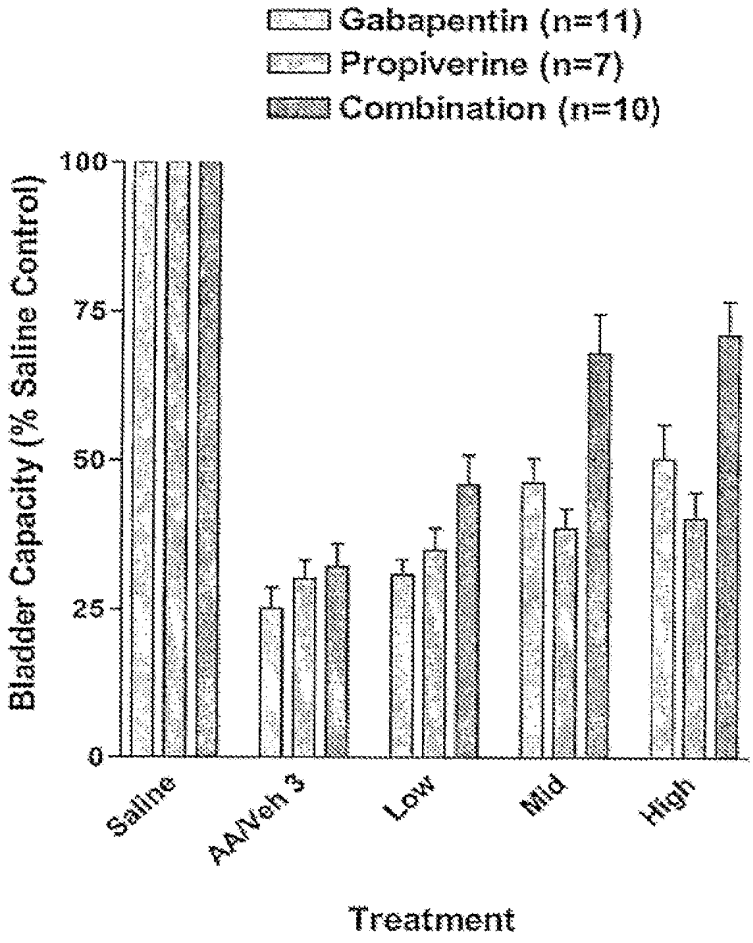
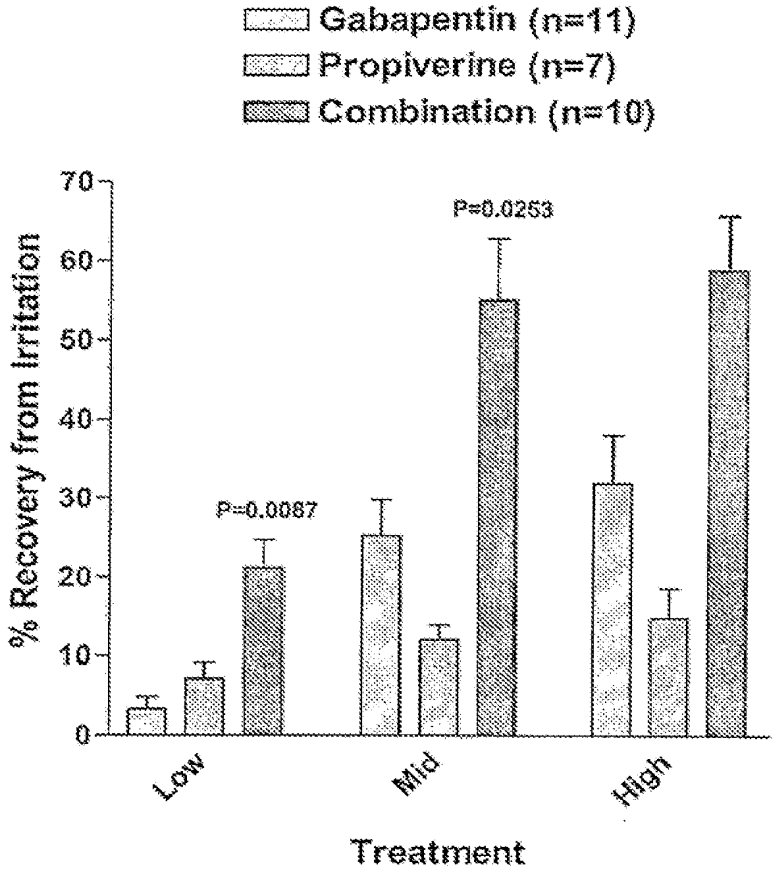

Gabapentin (n=11)
Propiverine (n=7)
Combination (n=10)
Bladder Capacity (% Saline Control)
100
75
50
25
0
Saline
AA/Veh 3
Low
Mid
High
Treatment

Figure 14



P=0.0067 for Synergy by 2-Way ANOVA

Figure 15

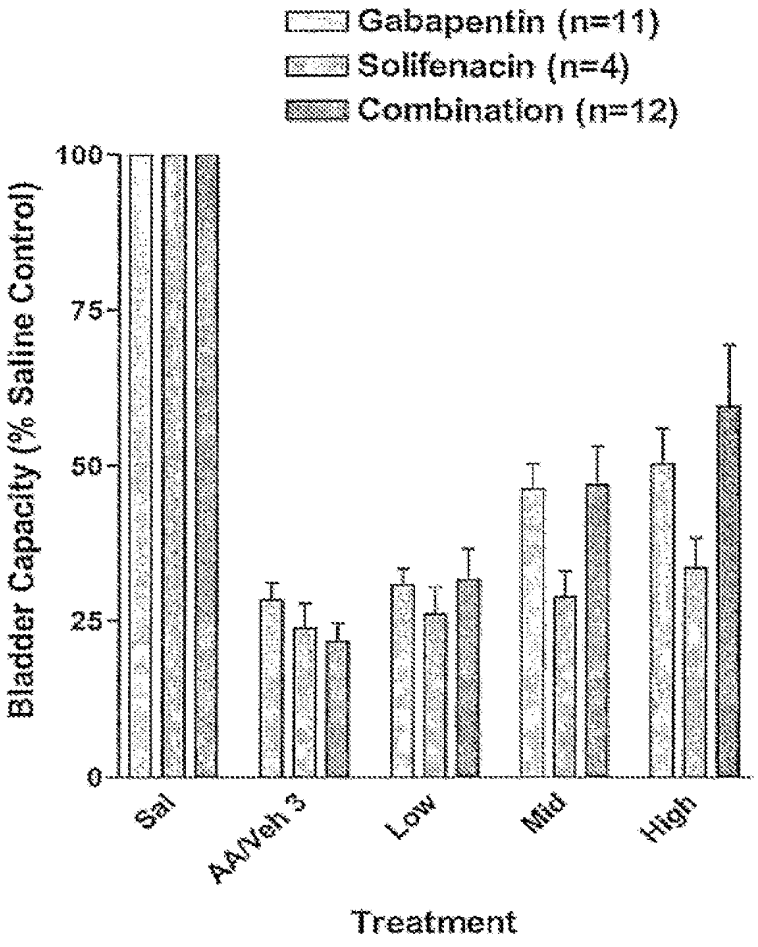
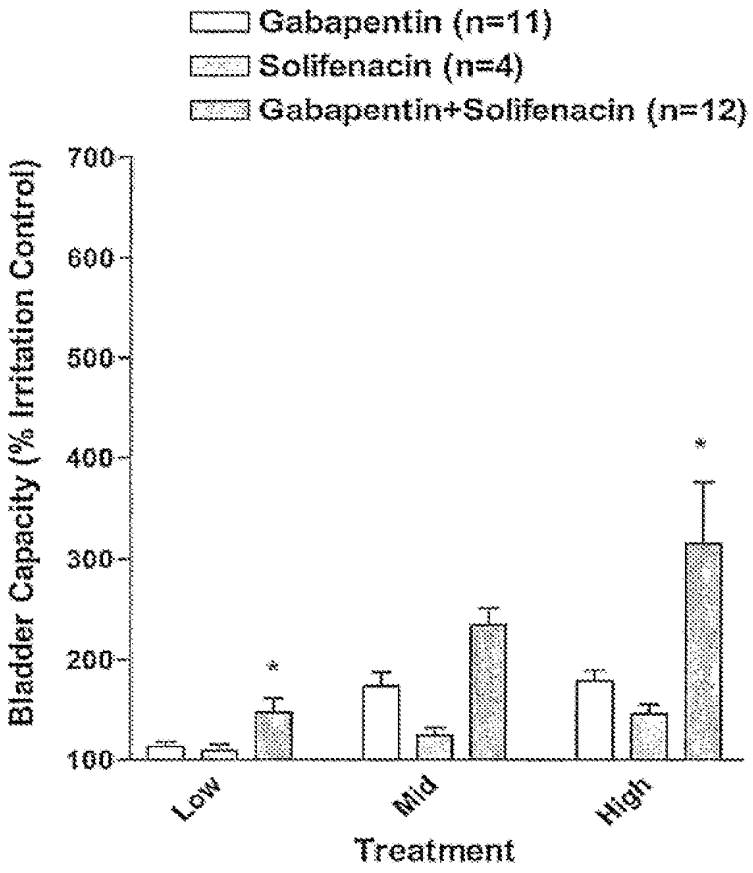
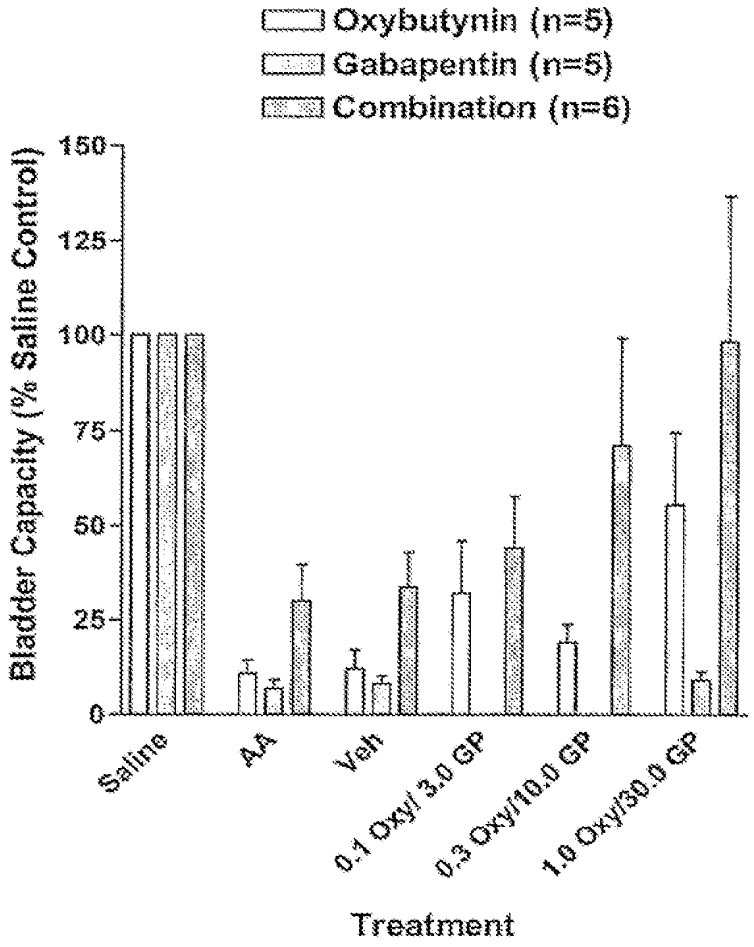

Gabapentin (n=11)
Solifenacin (n=4)
Combination (n=12)
Bladder Capacity (% Saline Control)
100
75
50
25
0
Sal
AA/Veh 3
Low
Mid
High
Treatment

Figure 16



* P<0.05 for Synergy by t Test
P=0.0022 for Synergy by 2-Way ANOVA

Figure 17



Drug doses (mg/kg) administered individually or in combination

Figure 18

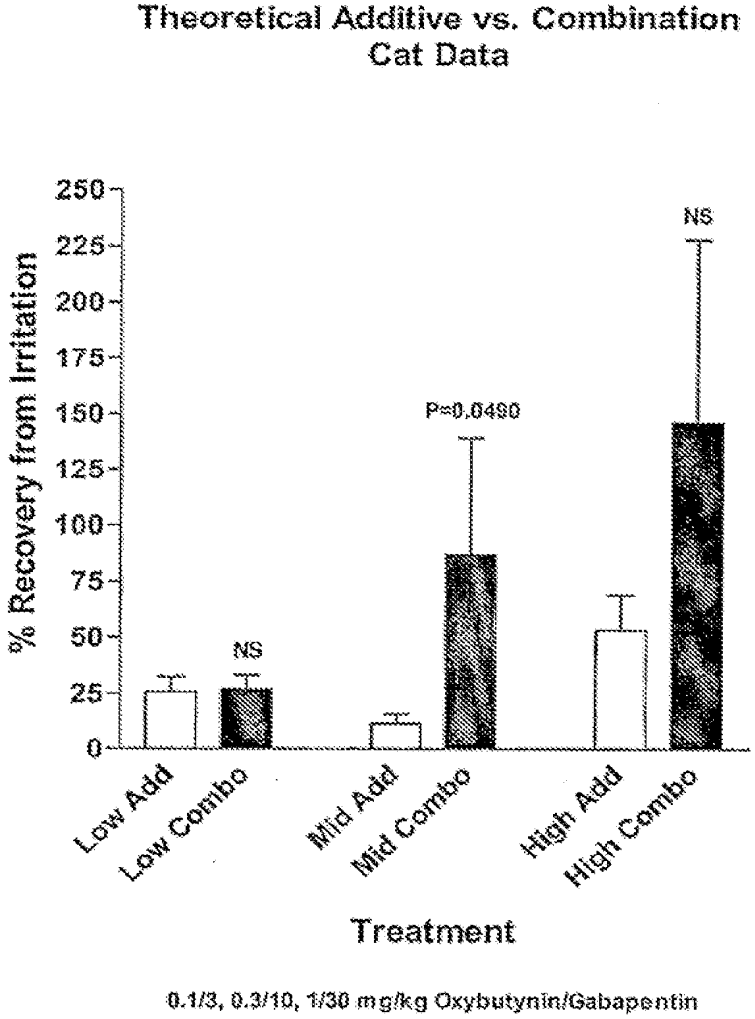
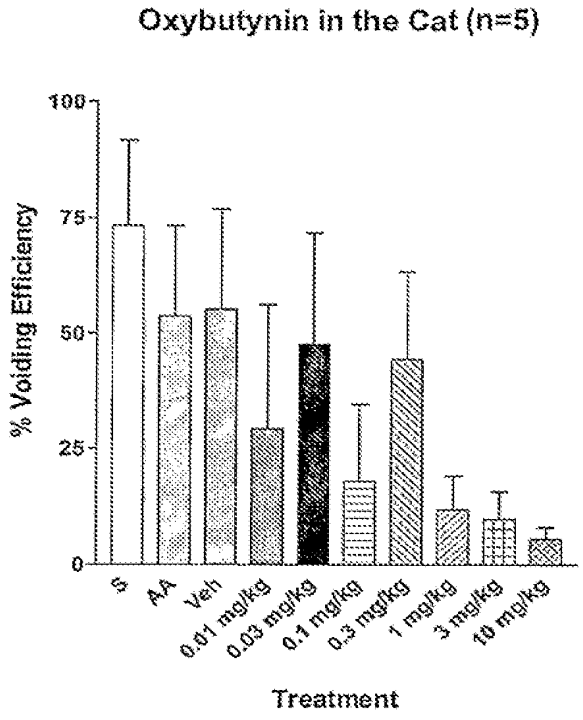
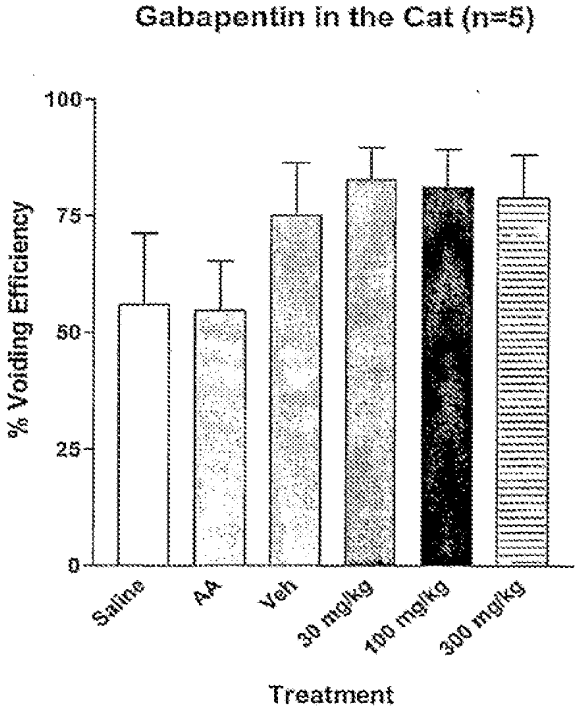

Theoretical Additive vs. Combination
Cat Data
% Recovery from Irritation
250
225
200
175
150
125
100
75
50
25
0
NS
P=0.0490
NS
Low Add
Low Combo
Mid Add
Mid Combo
High Add
High Combo
Treatment
0.1/3, 0.3/10, 1/30 mg/kg Oxybutynin/Gabapentin

Figure 19


Oxybutynin in the Cat (n=5)
% Voiding Efficiency
100
75
50
25
0
S
AA
Veh
0.01 mg/kg
0.03 mg/kg
0.1 mg/kg
0.3 mg/kg
1 mg/kg
3 mg/kg
10 mg/kg
Treatment

a.


Gabapentin in the Cat (n=5)
% Voiding Efficiency
100
75
50
25
0
Saline
AA
Veh
30 mg/kg
100 mg/kg
300 mg/kg
Treatment

b.

Figure 20

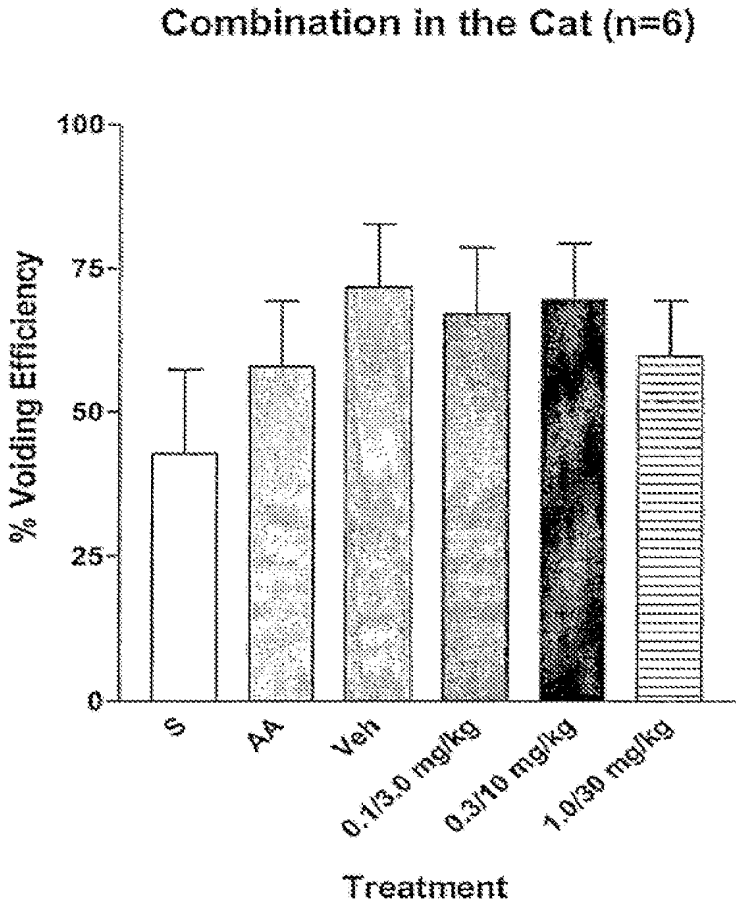

Combination in the Cat (n=6)
% Voiding Efficiency
100
75
50
25
0
S
AA
Veh
0.1/3.0 mg/kg
0.3/10 mg/kg
1.0/30 mg/kg
Treatment

Figure 21

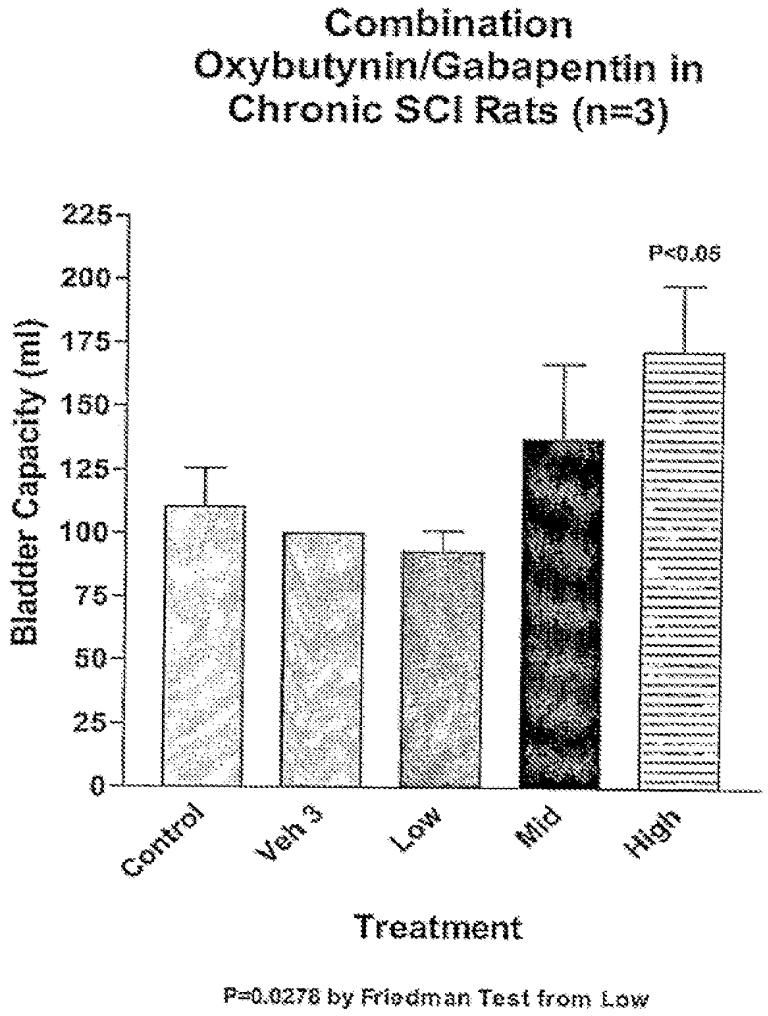

Combination
Oxybutynin/Gabapentin in
Chronic SCI Rats (n=3)
Bladder Capacity (ml)
225
200
175
150
125
100
75
50
25
0
P<0.05
Control
Veh 3
Low
Mid
High
Treatment
P=0.0278 by Friedman Test from Low

Figure 22

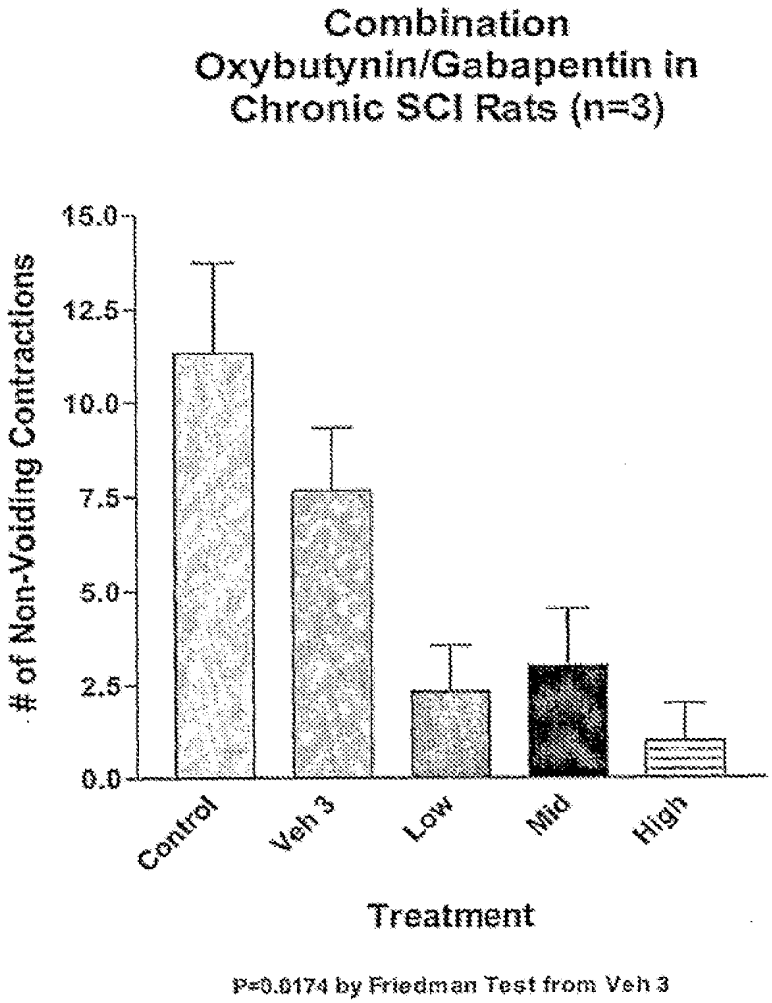
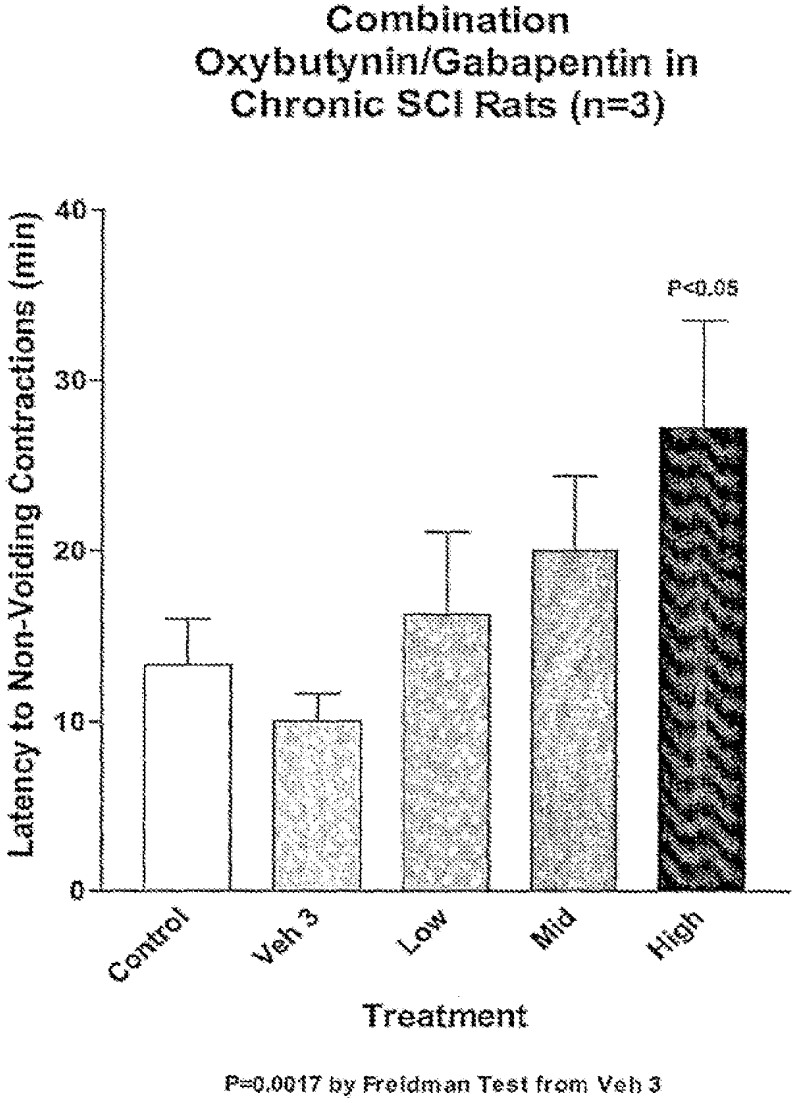

Combination
Oxybutynin/Gabapentin in
Chronic SCI Rats (n=3)
# of Non-Voiding Contractions
15.0
12.5
10.0
7.5
5.0
2.5
0.0
Control
Veh 3
Low
Mid
High
Treatment
P=0.0174 by Friedman Test from Veh 3

Figure 23


Combination
Oxybutynin/Gabapentin in
Chronic SCI Rats (n=3)
Latency to Non-Voiding Contractions (min)
40
30
20
10
0
P<0.05
Control
Veh 3
Low
Mid
High
Treatment
P=0.0017 by Freidman Test from Veh 3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/008605

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/195 A61K31/216 A61K31/197 A61K31/137 A61K31/445 A61K31/4725
//(A61K31/216,31:197),(A61K31/216,31:195),(A61K31/197,31:137)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, EMBASE, BIOSIS, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FIELD MARK J ET AL: "Gabapentin and the neurokinin1 receptor antagonist CI-1021 act synergistically in two rat models of neuropathic pain." JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 303, no. 2, November 2002 (2002-11), pages 730-735, XP002294267 ISSN: 0022-3565 abstract page 733; figure 3 page 734; figure 4	28,38, 39,41,42
X	WO 01/24792 A (HUGHES JOHN ; SINGH LAKHBIR (GB); WARNER LAMBERT CO (US)) 12 April 2001 (2001-04-12) page 12, lines 1-10 figures 2a-2f,3a-3b	28,38, 39,41,42

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 August 2004	09/09/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Rodriguez-Palmero, M

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/008605

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/01983 A (SINGH LAKHBIR ; WARNER LAMBERT CO (US); BRUMMEL ROGER N (US)) 11 January 2001 (2001-01-11) page 2, lines 11-15 figures 1,4	28,38, 39,41,42
X	WO 03/000642 A (NICOX SA ; DEL SOLDATO PIERO (IT); ONGINI ENNIO (IT)) 3 January 2003 (2003-01-03) page 1, paragraph 1 page 13, lines 1,2 page 18, paragraph 3 - paragraph 6 page 30; example 3	28,38, 39,41,42
X	DE SARRO G ET AL: "Gabapentin potentiates the antiseizure activity of certain anticonvulsants in DBA/2 mice." EUROPEAN JOURNAL OF PHARMACOLOGY. 22 MAY 1998, vol. 349, no. 2-3, 22 May 1998 (1998-05-22), pages 179-185, XP002291581 ISSN: 0014-2999 page 182; tables 2,3	28,38, 39,41,42
X	WO 01/37832 A (AVENTIS PHARMA SA) 31 May 2001 (2001-05-31) page 5, table claims	28,38, 39,41,42
X	WO 96/37202 A (ALZA CORP) 28 November 1996 (1996-11-28) page 5, lines 19-21	37
A	OBERPENNING F ET AL: "Interstitial cystitis: An update" CURRENT OPINION IN UROLOGY 2002 UNITED KINGDOM, vol. 12, no. 4, 2002, pages 321-332, XP009034871 ISSN: 0963-0643	10-14, 28-36, 38-43
X	page 326, column 1, paragraph 3	1-9, 15-27
A	KATZUNG BG: "Basic & Clinical Pharmacology, Eighth edition" 2001, LANGE MEDICAL BOOKS/MCGRAW-HILL , UNITED STATES OF AMERICA , XP002291582 page 457, column 2, last paragraph - page 458, column 2, paragraph 1 page 459, column 2, paragraph 3	28,38, 39,41,42

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/008605

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 03/070237 A (TAYLOR CHARLES PRICE JR ; WARNER LAMBERT CO (US)) 28 August 2003 (2003-08-28) page 2, lines 23-32 page 81, line 31 - page 82, line 8 page 84, line 16 - page 85, line 17	28,38, 39,41;42
E	WO 2004/054560 A (WESTBROOK SIMON LEMPRIERE ; TAYLOR CHARLES PRICE JR (US); WARNER LAMBE) 1 July 2004 (2004-07-01) page 6, paragraph 4 page 15, last paragraph - page 16, paragraph 6 claims 1,2,16	1-13, 17-28, 38,39, 41,42
A	FELIX R: "Voltage-dependent Ca<2+> channel 'alpha!2'delta! auxiliary subunit: Structure, function and regulation" RECEPTORS AND CHANNELS 1999 NETHERLANDS, vol. 6, no. 5, 1999, pages 351-362, XP009034843 ISSN: 1060-6823 page 359, column 2, paragraph 2 - page 361, column 2, paragraph 1	1-36, 38-43

INTERNATIONAL SEARCH REPORT

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Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-27 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
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